GI Tumors

Carcinomas, Neuroendocrine Neoplasms and Mesenchymal and Lymphoid tumors

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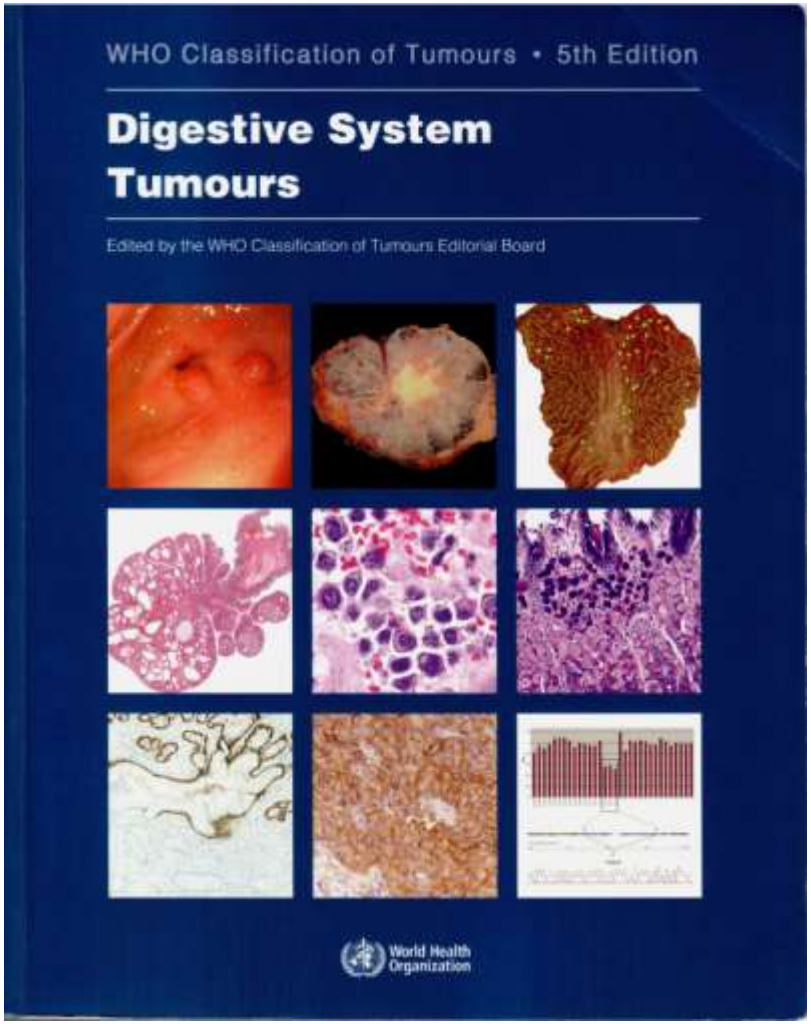
Tumors of the Digestive System

Part I: Carcinomas of the GIT

Part II: Neuroendocrine, mesenchymal and lymphoid neoplasms

Acknowledgement

Material from the Worldwide Web, the WHO book on Digestive System tumors and the scientific literature has been used in this presentation. These sources are acknowledged

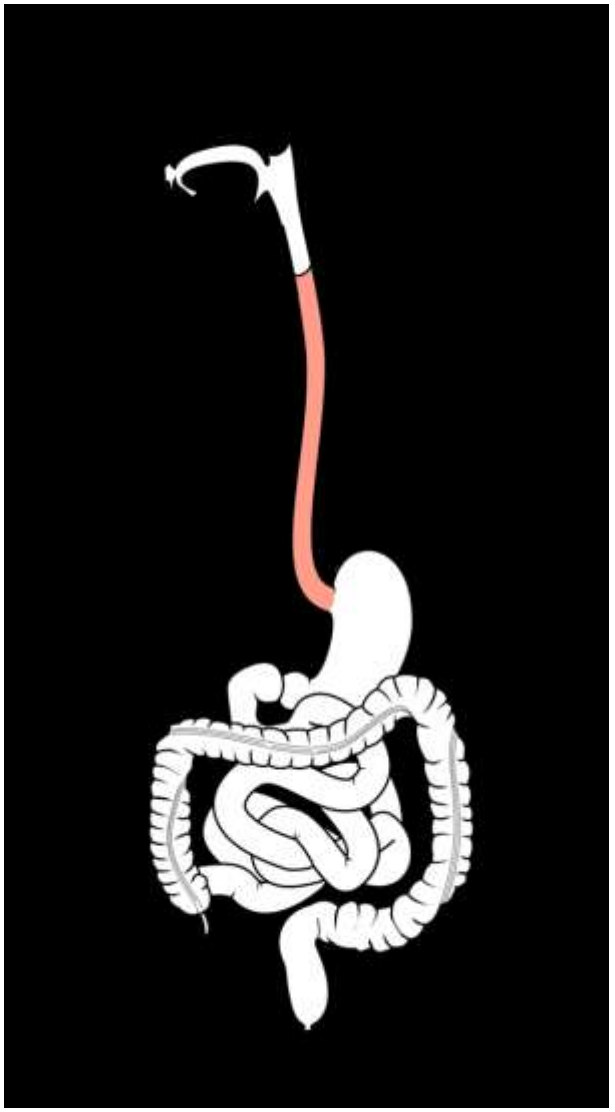

WHO Classification of Tumours • 5th Edition
Digestive System Tumours
Edited by the WHO Classification of Tumours Editorial Board
World Health Organization

WHO Classification Digestive System tumors

- **Epithelial tumors**
  - Carcinomas
  - Neuroendocrine neoplasms (NEN)
  - Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN)
- **Mesenchymal tumors**
  - GIST, sarcoma, other tumors
- **Lymphoid neoplasms**
- **Miscellaneous tumors**

WHO classification of epithelial and neuroendocrine tumors of the esophagus

- Adenocarcinoma NOS
- Adenoid cystic carcinoma
- Mucoepidermoid carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma NOS
  - Verrucous squamous cell carcinoma
  - Squamous cell carcinoma, spindle cell
  - Basaloid squamous cell carcinoma
- Carcinoma, undifferentiated, NOS
  - Lymphoepithelioma-like carcinoma
- Neuroendocrine tumour NOS
  - Neuroendocrine tumour, grade 1
  - Neuroendocrine tumour, grade 2
  - Neuroendocrine tumour, grade 3
- Neuroendocrine carcinoma NOS
  - Large cell neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
- Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)
  - Combined small cell–adenocarcinoma
  - Combined small cell–squamous cell carcinoma



Esophageal carcinomas

Squamous cell carcinoma (SCC)

SCC NOS, Verrucous SCC,
spindle cell SCC, basaloid SCC

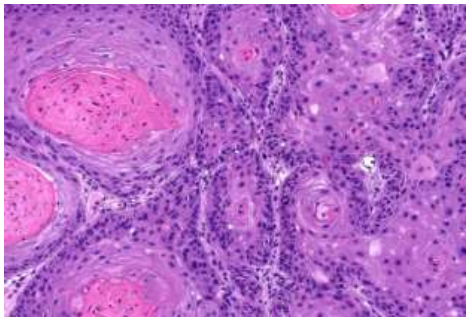
Adenocarcinoma NOS

Salivary gland tumors

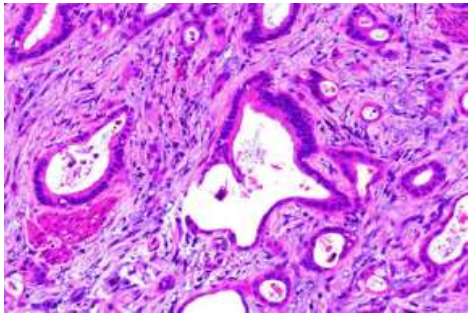
- Adenoid cystic carcinoma
- Mucoepidermoid carcinoma

Adenosquamous carcinoma

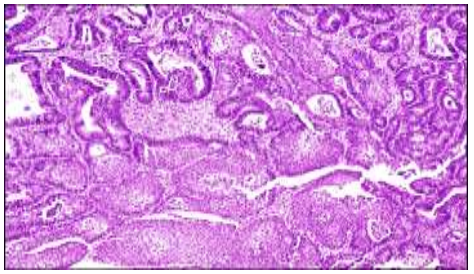
Undifferentiated carcinoma



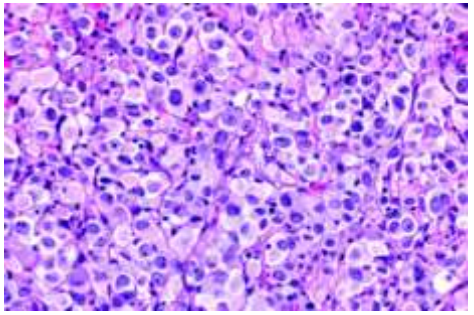
Squamous cell carcinoma



Adenocarcinoma



Adenosquamous carcinoma



Undifferentiated carcinoma

Squamous Cell Carcinoma of the esophagus

Incidence of esophageal SCC can vary by a **100-fold** between and within regions and countries being much more common in **rural and underdeveloped areas** of certain countries than in Western countries

Highest incidence regions include **Asia, South American and Sothern Africa**

Risk factors include **alcohol and tobacco, nutritional deficiencies and carcinogens** (polycyclic hydrocarbons, nitrosamines, etc)

SCC of the esophagus in the US is most frequent in **African American males** with male to female ratio of 4:1

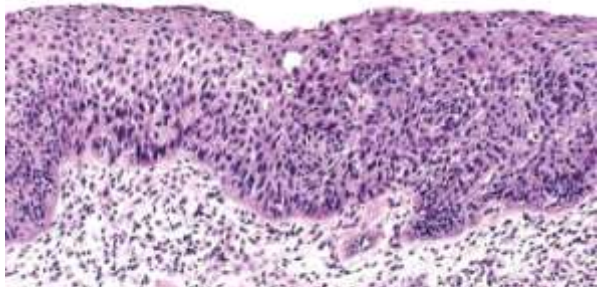
Evolution of SCC of the esophagus

SCC begins as squamous dysplasia which can progresses to squamous cell carcinoma in situ and then invasive squamous cell carcinoma

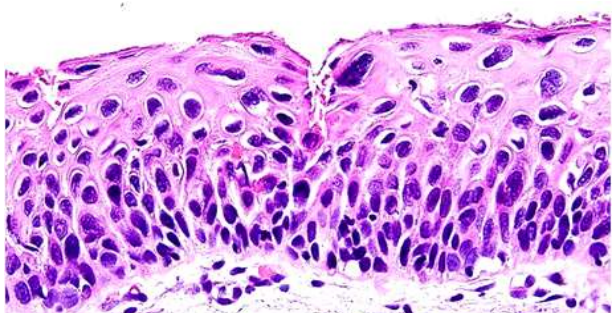
Endoscopically, early lesions appear as small gray-white plaque-like thickenings

Increased use of endoscopic "screening" has led to earlier diagnosis (superficial SCC)

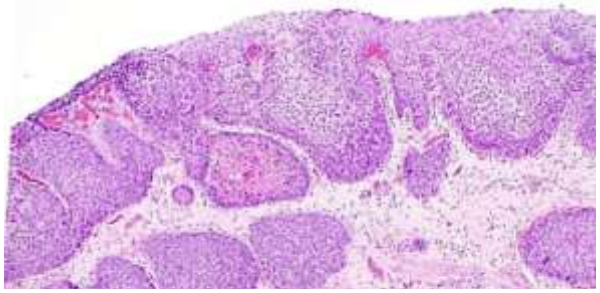
Early detection is critical (5-year survival rates are 75% for patients with superficial carcinoma) but drops to about 10% in patients with more advanced tumors



Squamous dysplasia



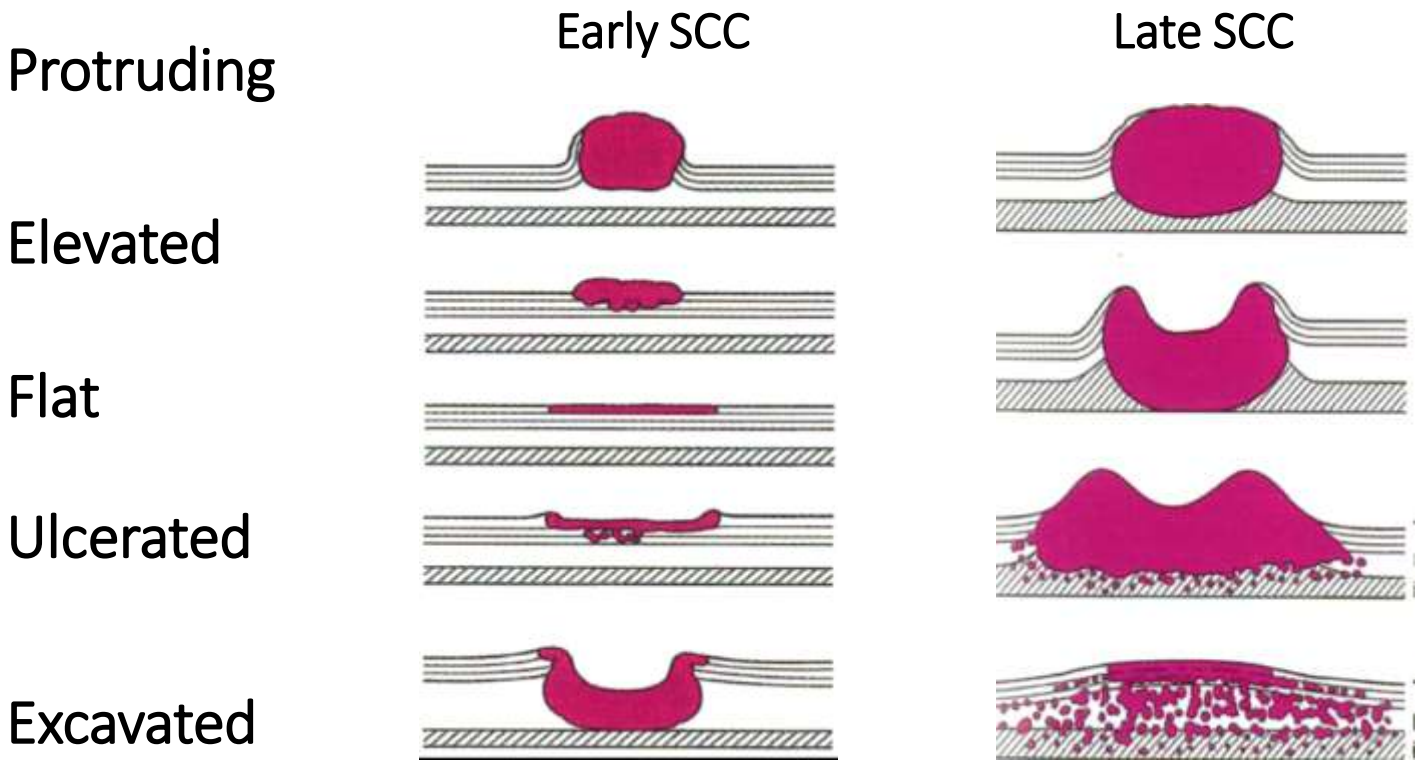
SCC in situ



Early SCC

Superficial squamous cell carcinoma of the esophagus

- Cancer locally confined to the mucosa and submucosa regardless of nodal status
- First identified in screening programs in China and Japan
- Currently superficial SCC accounts for up to 25% of resected esophageal SCCs in the US and Western Europe



Adenocarcinoma of the esophagus

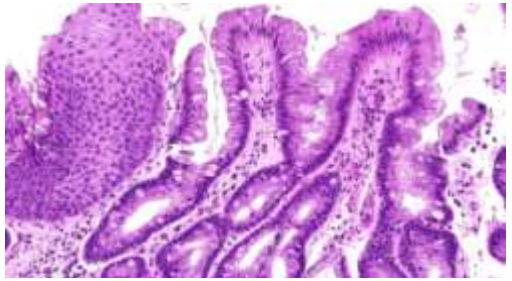
More common in western countries than in underdeveloped regions

Incidence in western countries has increased 10 folds since 1970

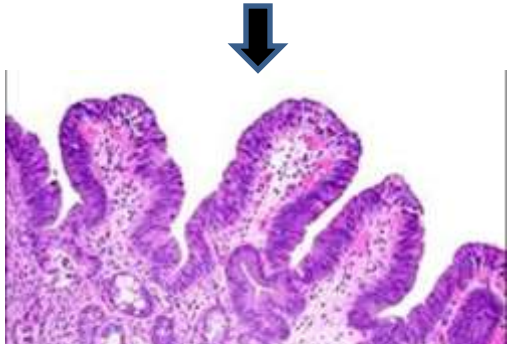
Typically arises in a background of Barrett esophagus and GERD

Risk factors include dysplasia in Barrett esophagus, smoking, obesity

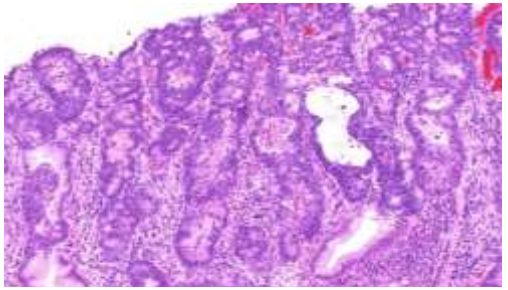
Most frequent in white American males with male to female ration of 7:1



BE, no dysplasia



BE with dysplasia



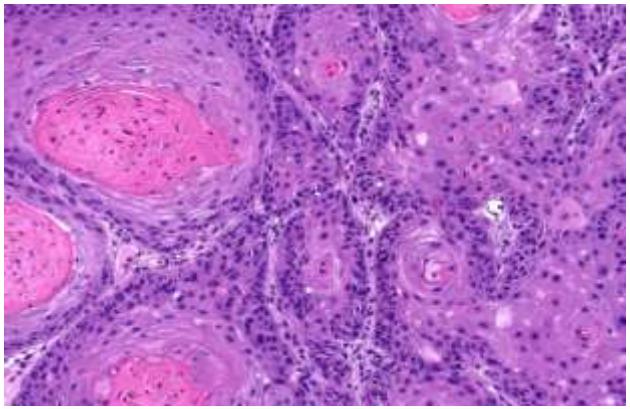
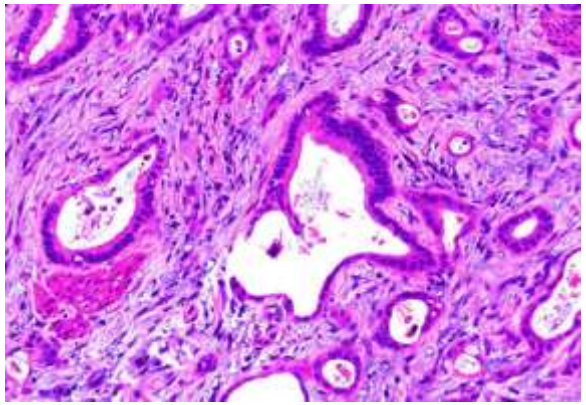
BE with adenocarcinoma

Main esophageal carcinomas		
Type	**Squamous cell carcinoma**	**Adenocarcinoma NOS**
Risk Factor	Smoking, drinking, nutritional deficiencies & others including HPV	Barrett esophagus & GERD, obesity, smoking
Epidemiology	Common in Asia, Africa, South America	Common in Western countries
Age & sex (USA)	Middle age & older males African Americans	Middle age & older males White Americans
Symptoms	Dysphagia, odynophagia, obstruction, vomiting, weight loss (cachexia), hemorrhage and sepsis (fistula)	
Location	Mostly in the middle (55%) and lower esophagus (35%)	Lower esophagus (>80%)
Survival	10% overall (75% early in early cancer)	25% overall (80% in early cancer)

Esophageal squamous cell carcinoma is broad spectrum cytokeratin and p40 positive

Esophageal adenocarcinoma is usually CK7 positive; CK20 negative

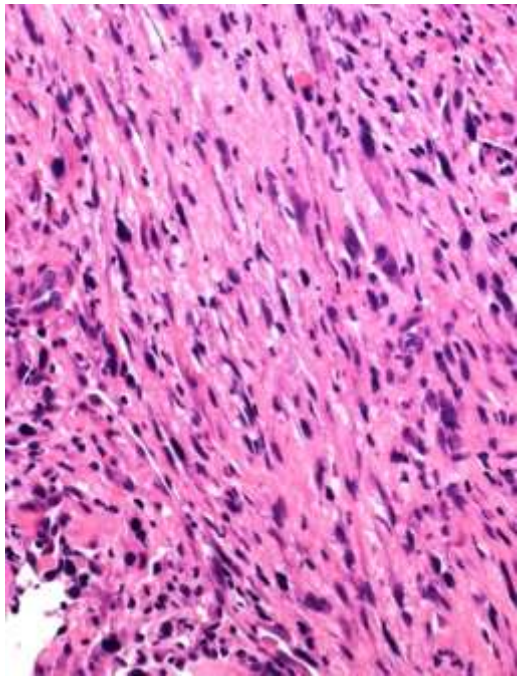
Carcinoma of the esophagus

Type	Squamous cell carcinoma	Adenocarcinoma
Macroscopic		
Microscopic		

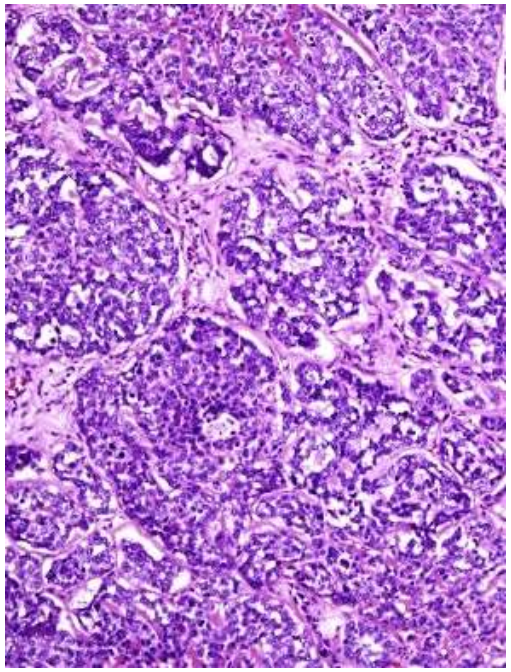
Squamous cell carcinoma variants

- Verrucous squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Basaloid squamous cell carcinoma

Verrucous SCC
Favorable



Spindle cell SCC



Basaloid SCC
Unfavorable

Cytokeratin (broad spectrum) and p40

WHO classification of epithelial tumors of the stomach

Adenocarcinoma NOS

- Mucinous-type
- Signet ring cell-type
- Medullary-type
- Intestinal-type
- Pancreatobiliary-type
- Tubular-type

Neuroendocrine neoplasms

Mixed neuroendocrine-non-neuroendocrine (MiNEN)

Lauren classification of gastric carcinoma

Intestinal type adenocarcinoma

Distal location with nodular growth pattern
Older people with M:F ratio of 2:1
Caused by **environmental factors** (H pylori)
Better prognosis
Declining incidence
Chromosomal instability (CIN) type

Intestinal type

Diffuse adenocarcinoma

Proximal stomach with diffuse growth pattern
(leather-bottle or linitis plastica)
Younger people with M:F ration of 1:1
Genetic factors (CDH1 mutations)
Worse prognosis
Increasing incidence
Genomically stable (GS) type (p53 mutation)

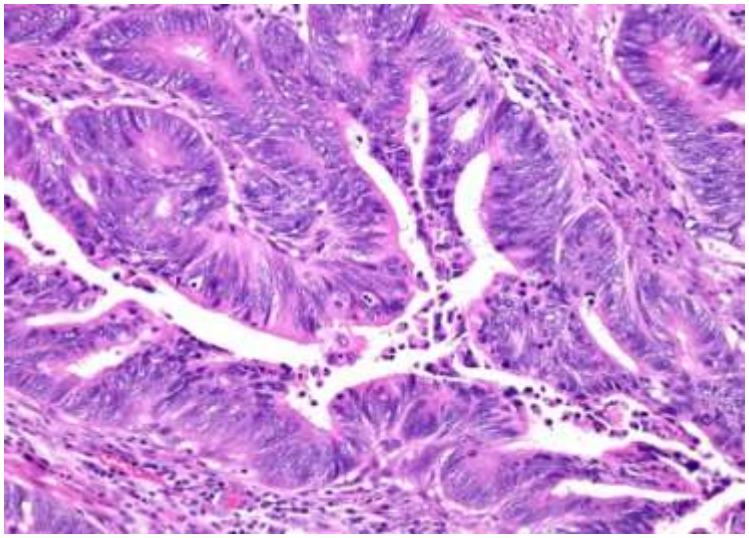
Diffuse type

Lauren classification was published in 1965
Lauren was a Swedish pathologist

Lauren classification of gastric carcinoma

Intestinal type adenocarcinoma

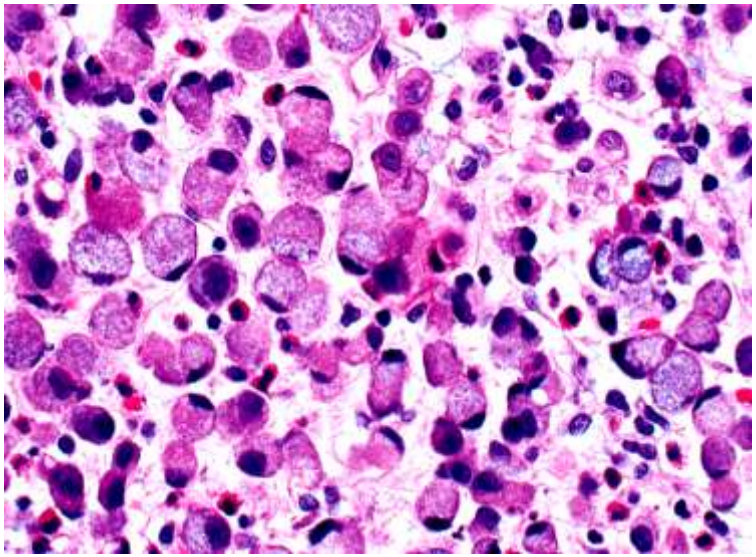
Glandular growth pattern
Intestinal type glands with mucin
Background of chronic **H pylori**
Gastritis with **intestinal metaplasia**



Intestinal type

Diffuse adenocarcinoma

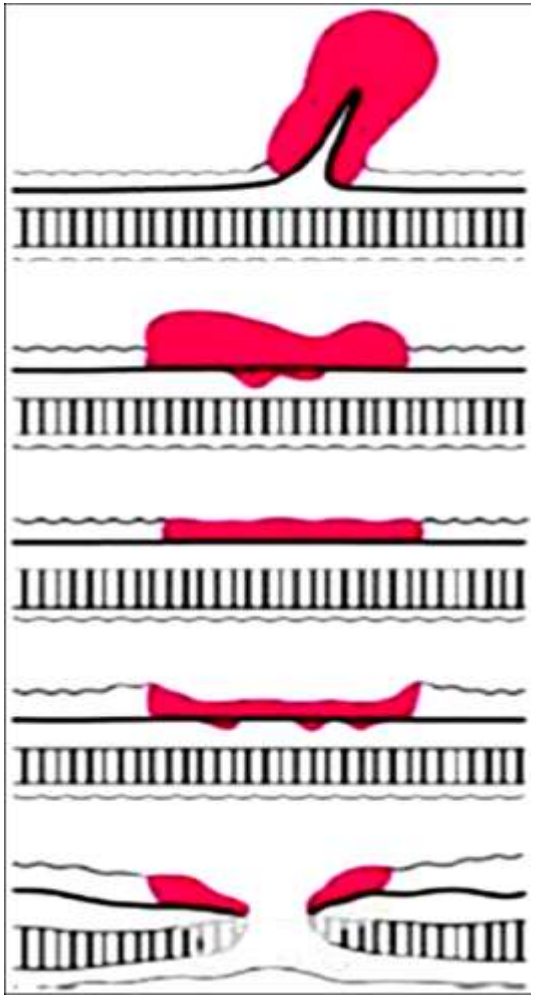
Single or small groups of cells
Cellular discohesion
Signet-ring appearance with cytoplasmic mucin droplets
No background gastric or H pylori



Diffuse type

Early gastric cancer

- Invasive adenocarcinomas confined to the mucosa and submucosa with no extension into the muscularis propria, regardless of nodal status or hepatic involvement (Japanese literature)
- Protruded, elevated, flat, depressed, excavated or combined
- Mostly in distal stomach with 10% being multicentric
- Histology is similar to late gastric adenocarcinoma
- Excellent results (cure rate of about 90%)
- Amendable to endoscopic treatment



Hereditary diffuse gastric cancer

Autosomal dominant cancer susceptibility syndrome

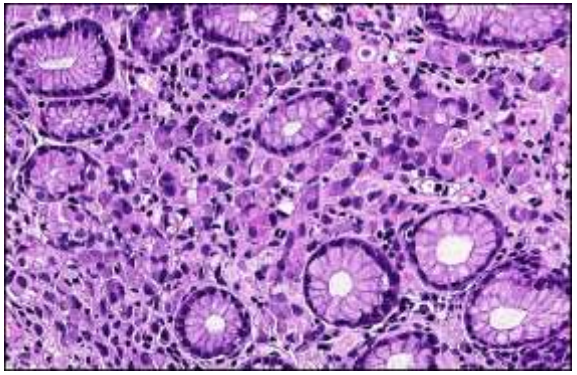
Signet-ring cell (diffuse) gastric cancer

Germline mutation in the E-Cadherin gene (CDH1) present in 30%

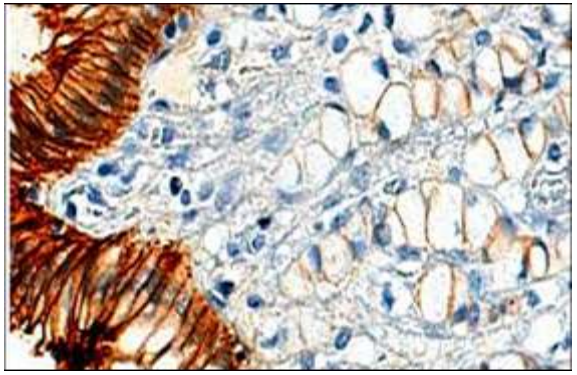
Absent or reduced expression for E-cadherin protein on IHC

Total gastrectomy for at-risk family members

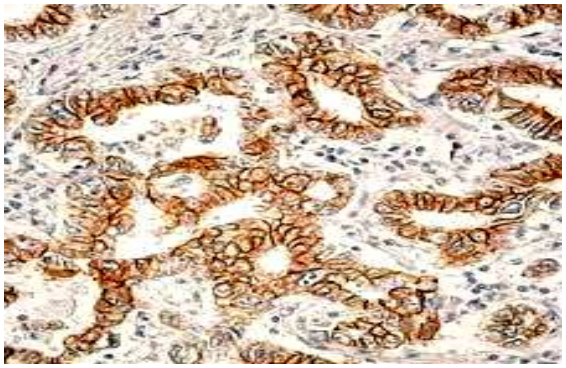
Hereditary diffuse gastric cancer



E-cadherin negative

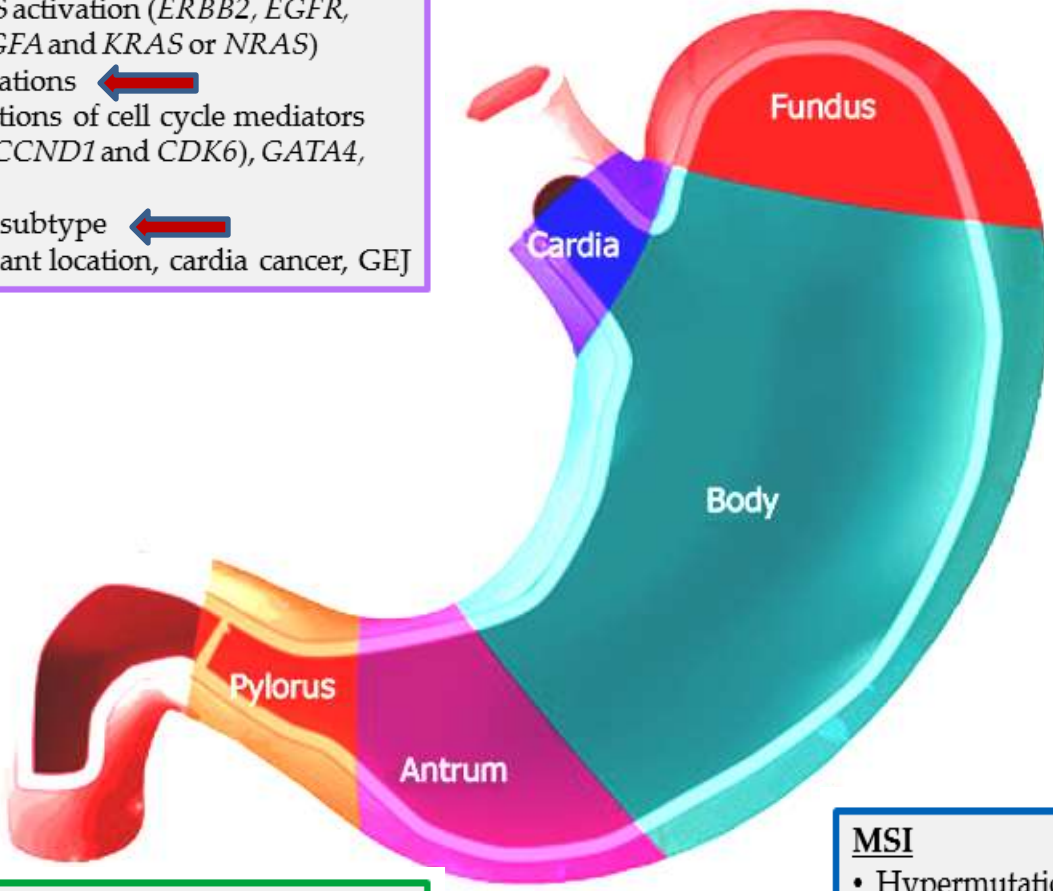


Intestinal gastric cancer E-cadherin positive



The Cancer Genome Atlas (TCGA) Project Molecular Classification 2013

Chromosomal instable (CIN) ~50%
- RTK–RAS activation (*ERBB2, EGFR, MET, VEGFA* and *KRAS* or *NRAS*)
- *TP53* mutations
- Amplifications of cell cycle mediators (*CCNE1, CCND1* and *CDK6*), *GATA4, GATA6*
- Intestinal subtype
- Predominant location, cardia cancer, GEJ



EBV ~10%
- DNA hypermethylation
- *PIK3CA* mutations (frequent)
- *PDL1* and *PDL2* overexpression
- Recurrent *JAK2* and *ERBB2* amplification
- *CDKN2A* silencing
- Immune cell signaling
- *ARID1A* and *BCOR* mutations (frequent)
- *TP53* mutations (rare)
- Intestinal subtype
- Predominant location corpus

Genomic stable ~20%
- *CDH1* and *RHOA* mutations
- *CLDN18–ARHGAP26* fusion
- Cell adhesion pathways (EMT)
- Younger patients
- Diffuse subtype

MSI ~20%
- Hypermutation
- *MLH1* silencing
- KRAS or NRAS activation
- *RASA1* and *PTEN* inactivation
- Mitotic pathways
- Older patients
- Intestinal subtype

IHC markers in gastric carcinoma	
Cytokeratins (CK7 and CK20)	Most gastric cancers are CK7 and CK20 positive; some are negative for both CK7 is often positive in gastric adenocarcinoma CK20 can be positive in intestinal-type gastric cancer
CDX2	Initially thought to be specific for colon carcinoma Frequently (>50%) expressed in intestinal-type (indicate lesser invasiveness)
E-cadherin loss	Associated with the more **aggressive diffuse gastric cancer**
HepPar-1	Marker for hepatocytes Positive in >50%, including signet-ring cell carcinoma
p53 protein	Useful in assessing dysplasia and is often mutated in the intestinal-type
HER2	Overexpression is a common and is associated with **aggressive disease** (targetable)
MSI	Identify a subtype that is associated with **better prognosis**
PD-L1	Expression level can help predict response to **immunotherapy (checkpoint inhibitors)**

Prognostic factors

Overall prognosis of gastric cancer is poor

Tumor stage is the most powerful determinant of prognosis

Histology is less important but survival is slightly higher in intestinal-type than diffuse and micropapillary types

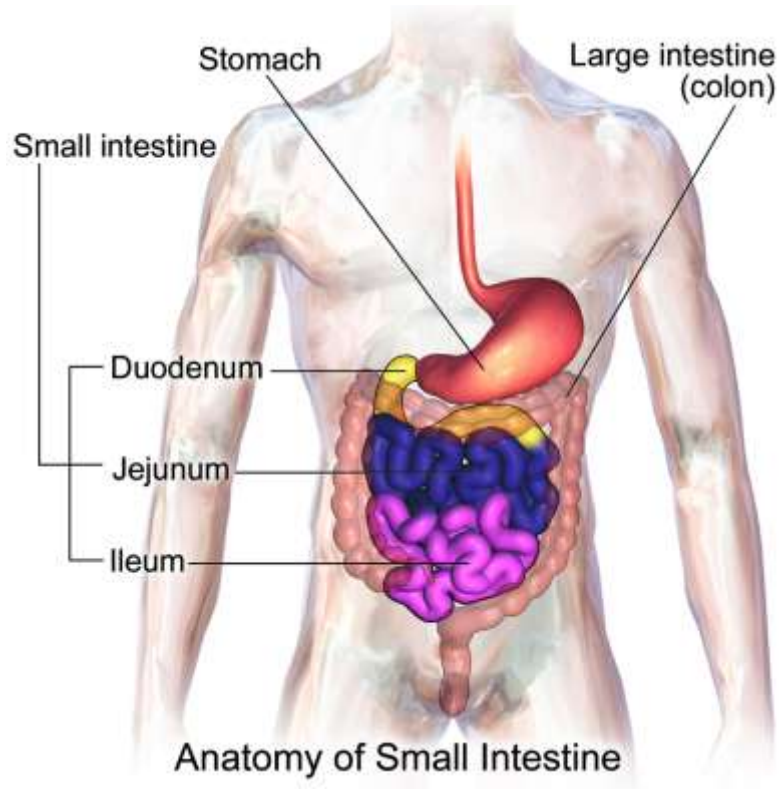
Adverse prognostic features include age (>70 years), proximal tumor location, lymphovascular space invasion and high CEA and CA19.9

Targeted therapy (HER2 and PDL1) may increase progression-free and overall survival

WHO classification of epithelial tumors of the small intestine

Malignant epithelial tumours

8140/3	Adenocarcinoma NOS
8480/3	Mucinous adenocarcinoma
8490/3	Signet-ring cell carcinoma
8510/3	Medullary carcinoma NOS
8144/3	Adenocarcinoma, intestinal type
8163/3	Pancreatobiliary-type carcinoma
8211/3	Tubular adenocarcinoma
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8153/3	Gastrinoma NOS
8156/3	Somatostatinoma NOS
8241/3	Enterochromaffin-cell carcinoid
8693/3	Extra-adrenal paraganglioma NOS
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)



Anatomy of Small Intestine

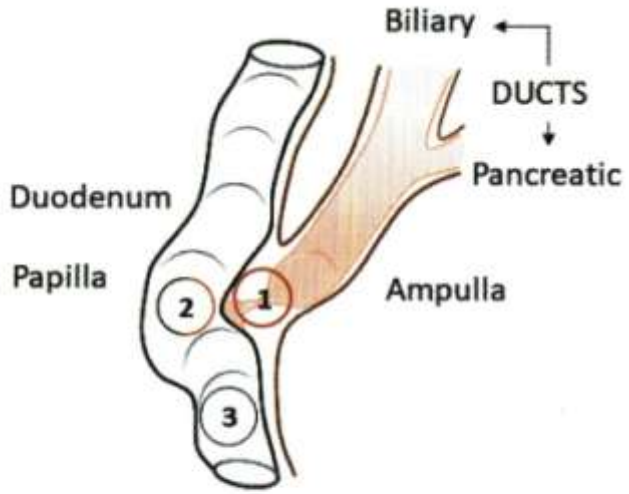
Carcinomas of the small intestine

Much less common than colorectal carcinomas

Predilection for the ampullary region

Prevalence decreases from the duodenum to ileum (**60% in the duodenum to 20% in the jejunum to 10% in the ileum)**

Duodenal cancer can be **periampullary, intra-ampullary or non-ampullary (extra-ampullary)**



1 Ampullary duct
2 Periampullary (duodenal) area
3 Extra-ampullary (duodenal) area

Carcinomas of the small intestine

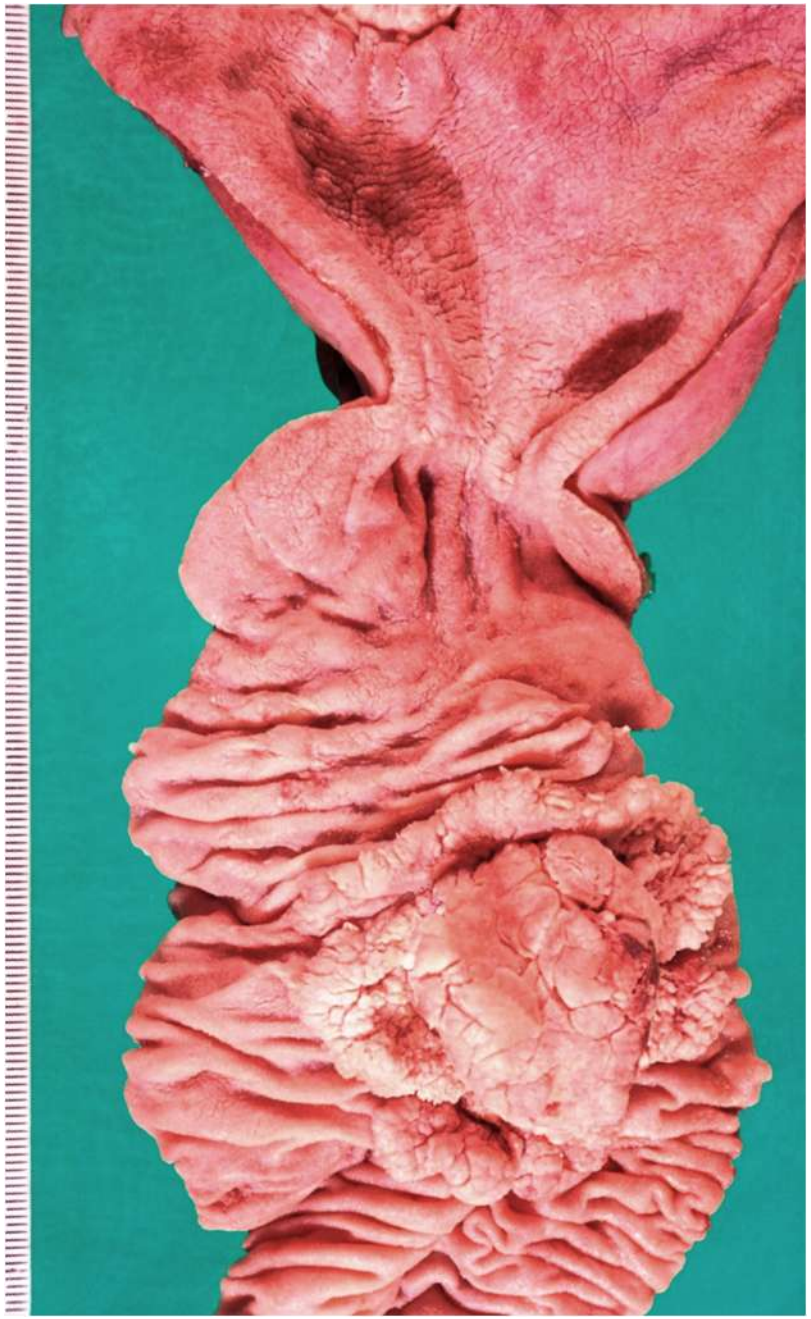
Most are sporadic (no apparent cause)
Some arise in the setting of chronic inflammation (Crohn disease and celiac disease) or seen in hereditary cancer syndromes (FAP)

Periampullary tumors produce **ulcerated or fungating masses**

Intra-ampullary tumors produce more subtle endoscopic abnormalities such as **slight elevations, nodularity or ulcers**

Non-ampullary tumors are **asymptomatic until locally advanced (bleeding or obstruction)**

Overall prognosis is poor except for periampullary tumors

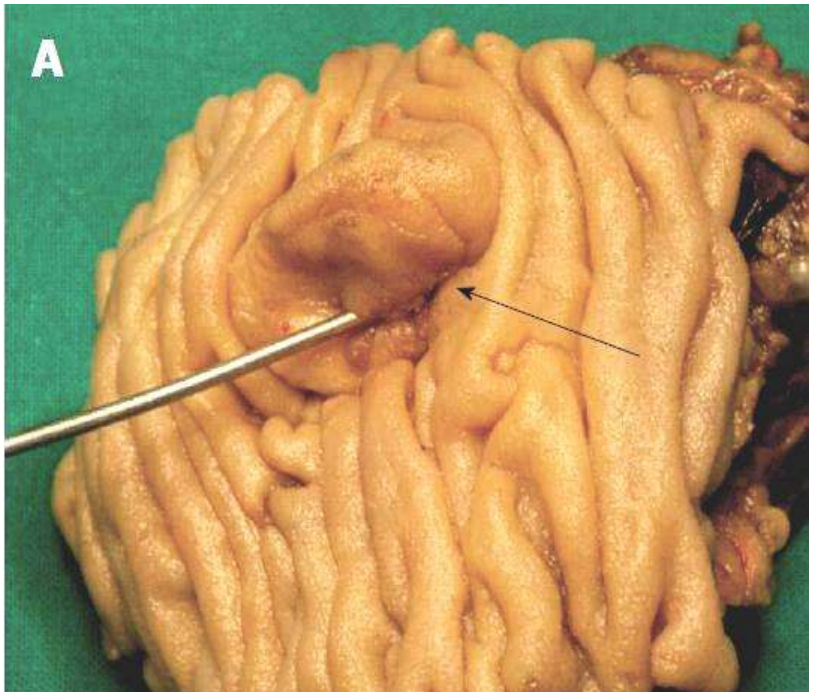


Ampullary and periampullary carcinomas

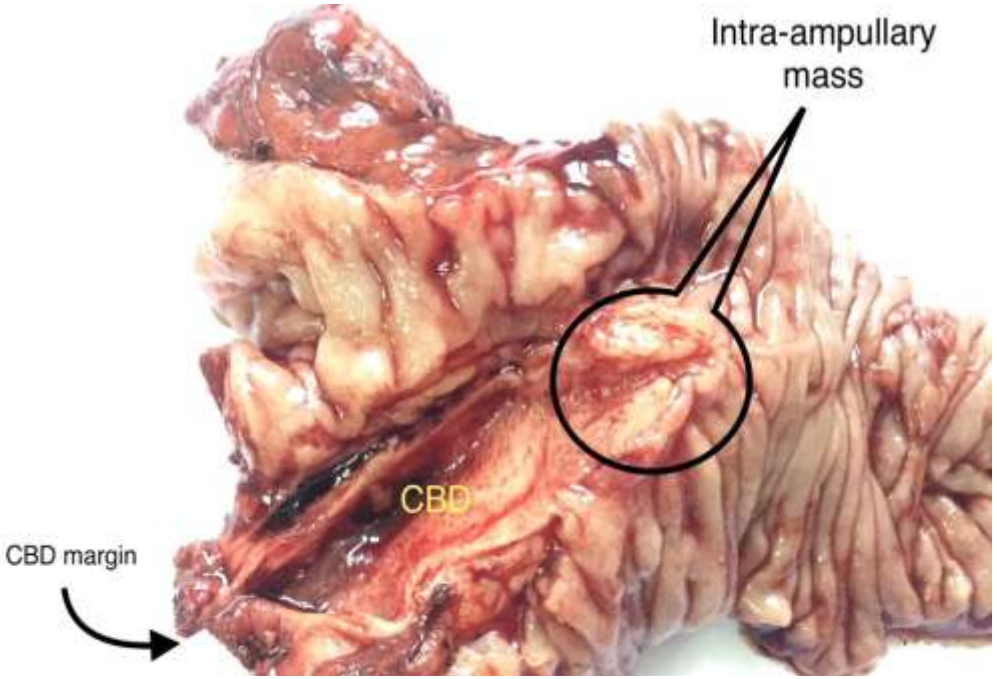
Most (90%) arise from intestinal-type adenomas

Present early due to biliary obstruction when they are still relatively small

Can occur as isolated lesions in older adults or in the setting of cancer syndromes such as FAP, Lynch syndrome, NF type 1, and MUTYH-associated polyposis



Ampullary carcinoma

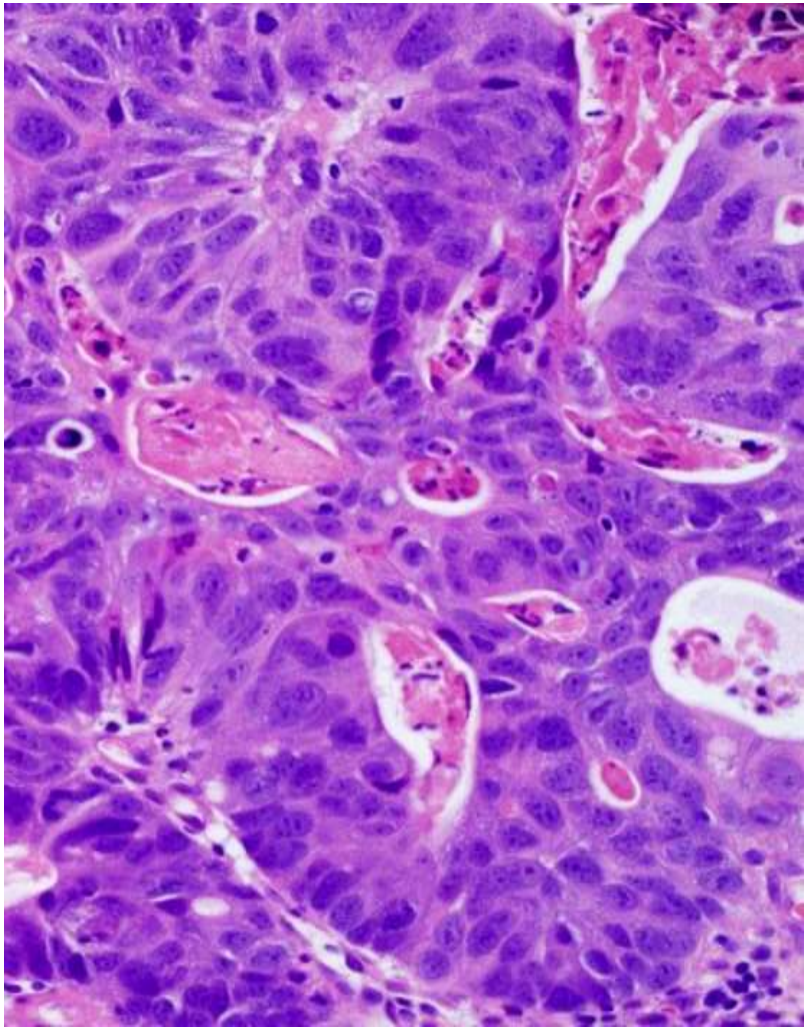


Intra-ampullary carcinoma

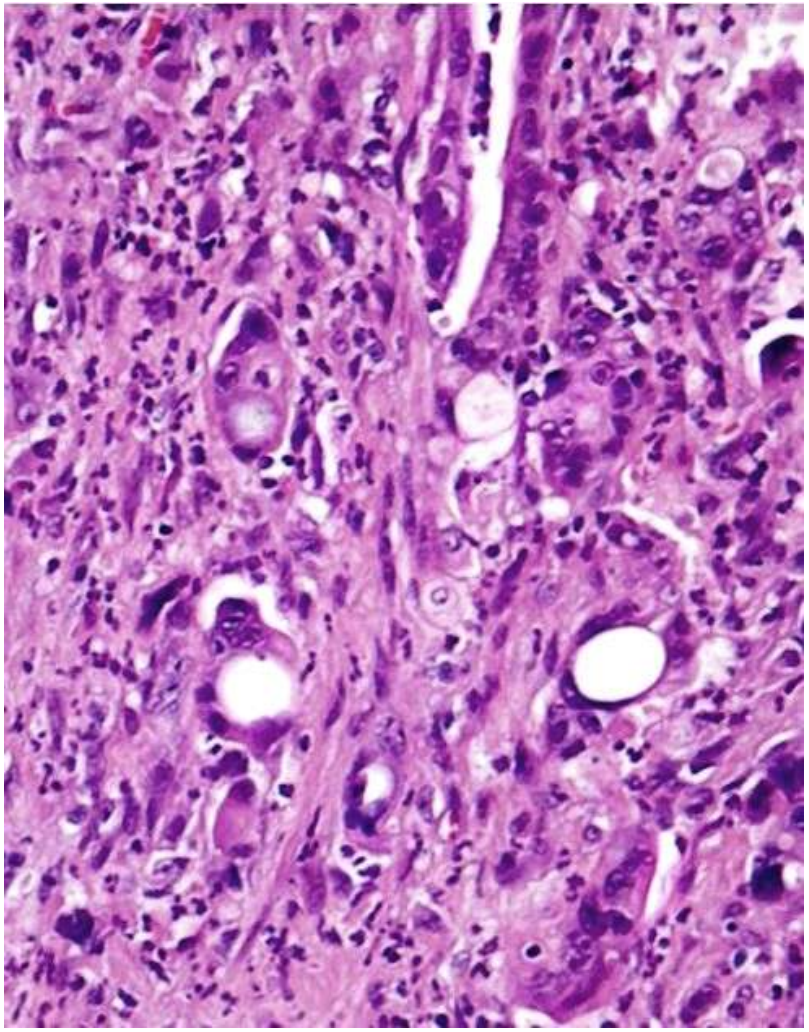
Non-ampullary carcinoma

Periampullary intra-ampullary carcinomas

Intestinal type



Pancreatobiliary type



classification of the immunohistochemical tumor types.

	Extrahepatic pancreatobiliary	Intestinal	Intrahepatic cholangiocarcinoma
CK19	+	+	+
CK20	-/+	+/-	-
MUC2	-	+/-	-
MUC5AC	+/-	-/+	-
CA19-9	+	+	+/-
mCEA	+/-	+	-
CA125	+/-	-/+	-
SMAD4	-/+	+	+

Summary of IHC markers in small bowel carcinoma	
Intestinal-type ampullary adenocarcinomas	Frequently express CDX-2 and MUC2 Variable expression of cytokeratins 7 and 20
Pancreatobiliary-type adenocarcinomas	Resemble those of pancreatic ductal adenocarcinomas and bile duct carcinomas **Positivity for cytokeratin 7** **Lack of staining for MUC2 and cytokeratin 20**
Approximately 65% of ampullary carcinomas harbor **TP53 mutations**	
MSI has been variably reported among ampullary carcinomas and is detected at rates **comparable to those seen in colorectal carcinomas**	

The MUC family of mucins

Encompasses both **neutral and acidic mucins**

MUC proteins can be **neutral or acidic** depending on their **glycosylation patterns**

Classification by charge

Neutral mucins lack acidic groups on their carbohydrate chains (no net charge)

Acidic mucins contain carboxylates or sulfates (negative charge at physiological pH)

Neutral mucins: MUC1 found in the surface epithelium of the stomach.

Acidic mucins: MUC2 (intestinal mucin) which is primarily considered acidic due to its high sialic acid content.

Histochemical staining: Special stains like Alcian blue can differentiate between neutral and acidic mucins based on their charge properties

GI mucins (MUCs)

Family of large heavily **glycosylated proteins**

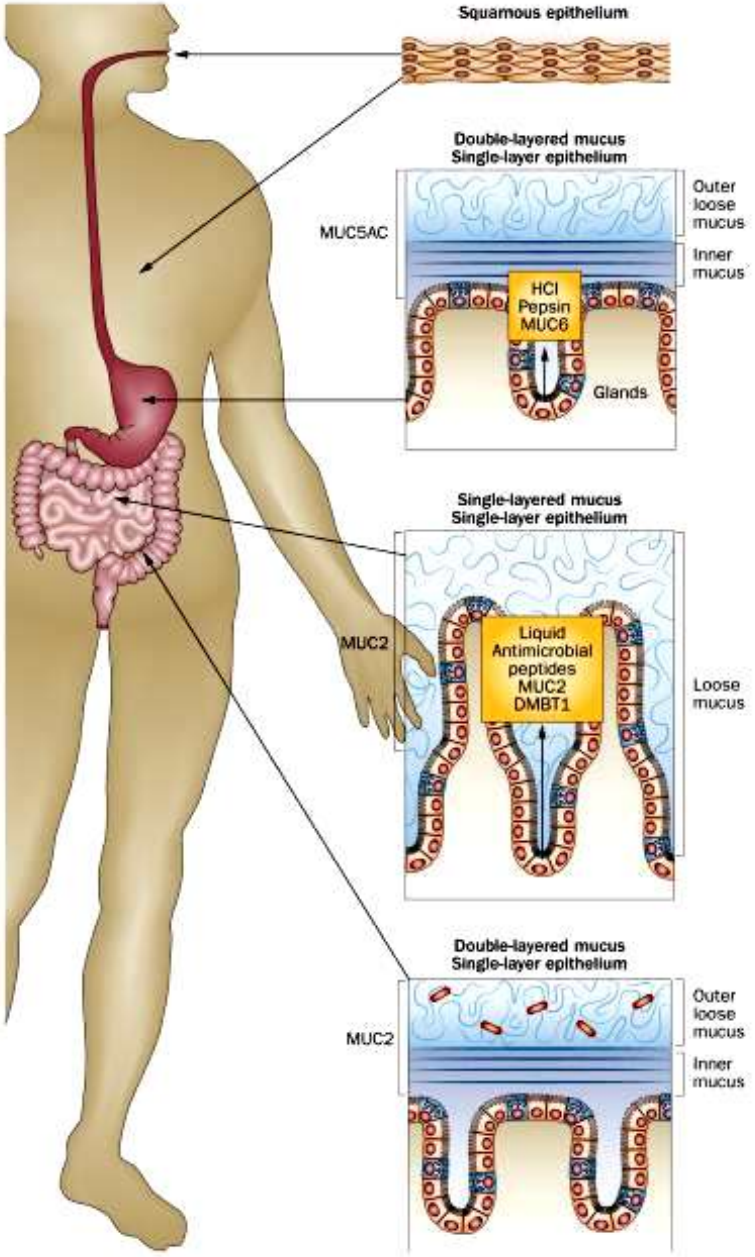
Attached mucin (transmembrane) or **unattached mucin** (secreted gel-forming)

Majority are **attached (transmembrane)** mucin, involved in **cell signaling and adhesion**

Some found on the **surface of epithelial cells**, acting as a **protective barrier**

Stomach and colon have a two-layered mucus system (inner attached mucus and outer unattached or loose) mucus layer.

Small intestine has only **one type of mucus** that is **unattached (loose)**



	Mouth	Stomach	Small intestine	Large intestine
Mucus layers	None	Outer, unattached layer Inner, attached layer	Single, unattached layer	Outer, unattached layer Inner, attached layer
Gel-forming mucins: • Surface/crypt • Gland • Paneth cells	NF MUC5B NA	MUC5AC MUC6 NA	MUC2 MUC6 MUC2	MUC2 (MUC5B) NF NA
Transmembrane mucins: • Epithelial cells	MUC1, MUC16	MUC1	MUC1, MUC3, MUC4, MUC12, MUC13, MUC17	MUC1, MUC3, MUC4, MUC12, MUC13, MUC17
Secreted mucins	MUC7	NF	NF	NF

NF = Not Found; NA = Not Available

GI Mucin System

Stomach - MUC1

Lubricates and protects from acids and enzymes and against microorganisms and toxins

Small bowel – MUC2

Traps and disarms bacteria which are then cleared by motor activity and fluid secretion

Large bowel (two-layered mucus system) – MUC2

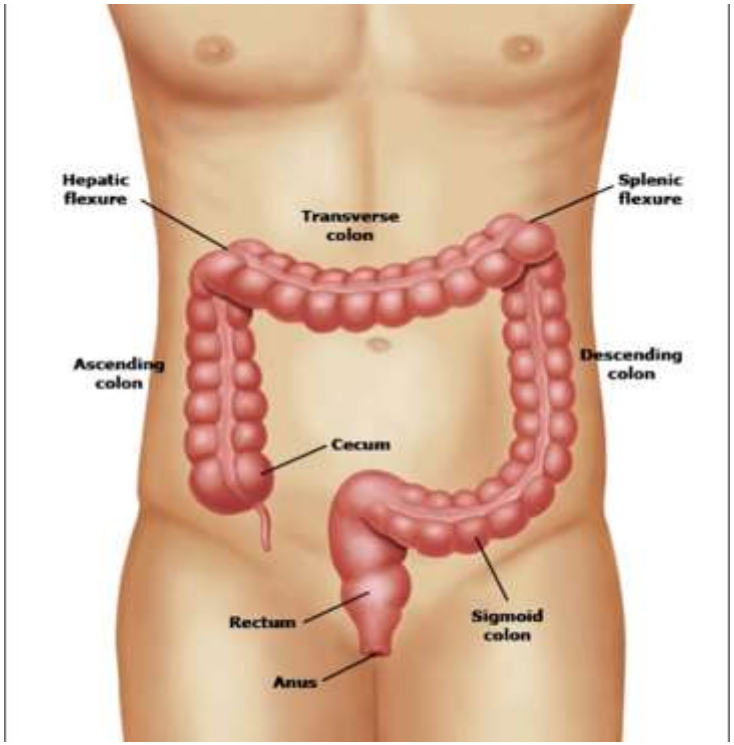
Inner layer is normally impenetrable to bacteria

Outer layer creates a well-defined space for beneficial bacteria to reside, fostering a harmonious relationship between the host and the microbiota and contributing to overall intestinal health

WHO classification of epithelial tumors of the colorectum

Malignant epithelial tumours

8140/3	Adenocarcinoma NOS
8213/3	Serrated adenocarcinoma
8262/3*	Adenoma-like adenocarcinoma
8265/3	Micropapillary adenocarcinoma
8480/3	Mucinous adenocarcinoma
8490/3	Poorly cohesive carcinoma
8490/3	Signet-ring cell carcinoma
8510/3	Medullary adenocarcinoma
8560/3	Adenosquamous carcinoma
8020/3	Carcinoma, undifferentiated, NOS
8033/3*	Carcinoma with sarcomatoid component
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8152/3	L-cell tumour
8152/3	Glucagon-like peptide-producing tumour
8152/3	PP/PYY-producing tumour
8241/3	Enterochromaffin-cell carcinoid
8241/3	Serotonin-producing tumour
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

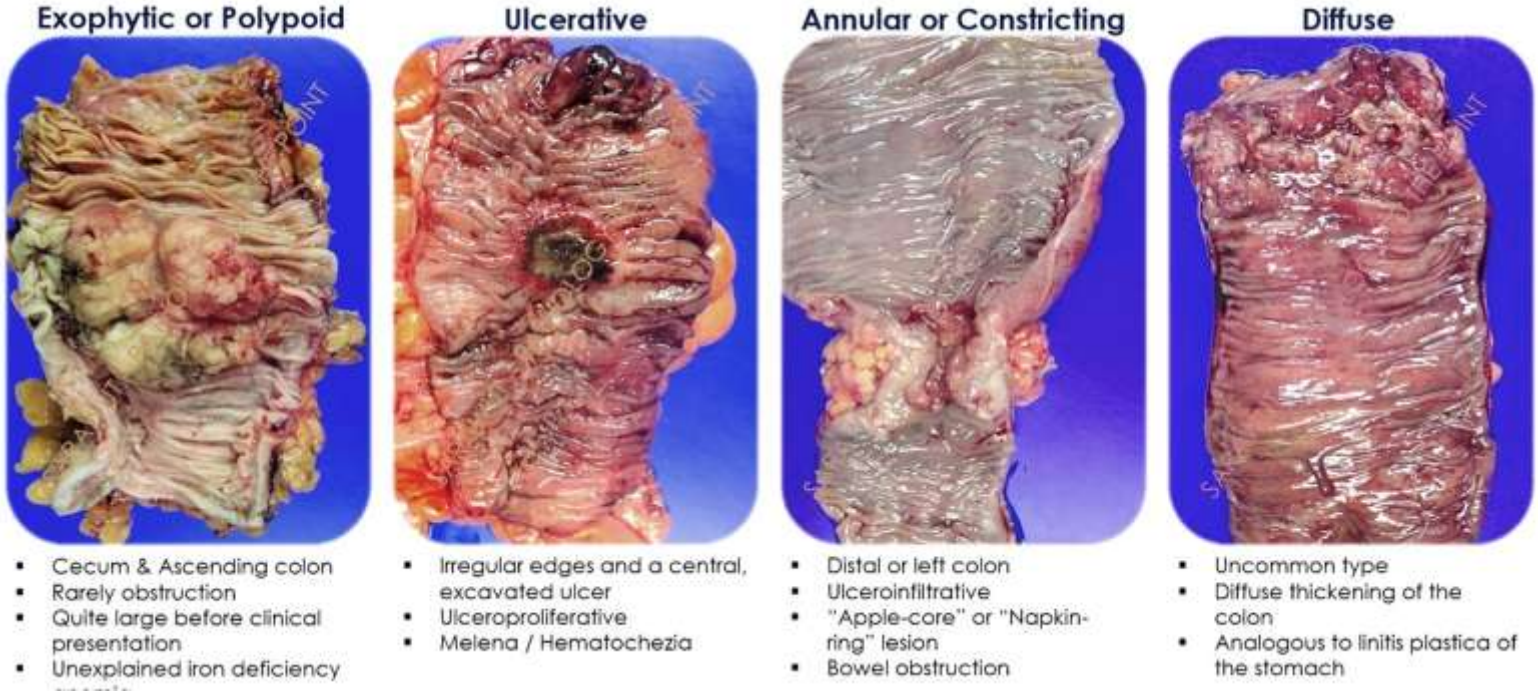


Colorectal carcinomas

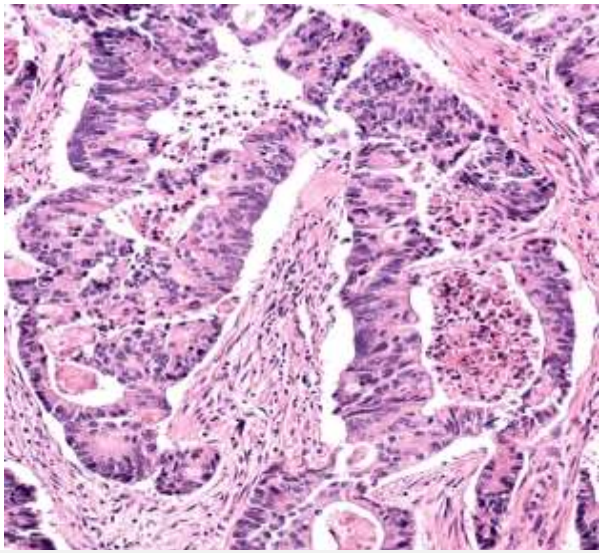
- Major cause of **morbidity and mortality** worldwide
- >500,000 new cases and >50,000 death each year in the US
- Cause **15% of all cancer-related deaths in the US**
- Incidence **peaks at 60 to 70 years** of age
- **Dietary factors** (processed food and high intake of refined carbohydrates and fat)
- **NSAIDs have a protective effect** through inhibition of COX-2 which is highly expressed in 90% of colorectal adenomas and carcinomas

Clinical features of colorectal cancer

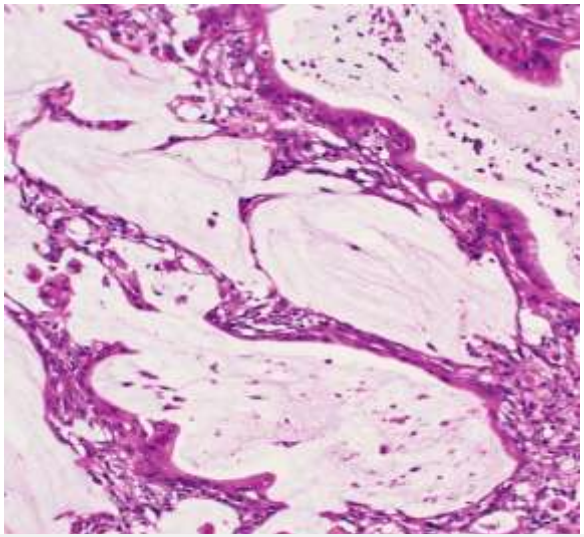
- Almost all are **adenocarcinomas**
- Most arise within **adenomas**
- Develop **slowly** and may go undetected for **long periods**
- **Right colon cancers** grow as **exophytic masses** and present with **fatigue and weakness** (iron deficiency anemia)
- **Left colon cancers** grow as **constricting lesions** and may produce occult bleeding, bowel habit change or obstruction



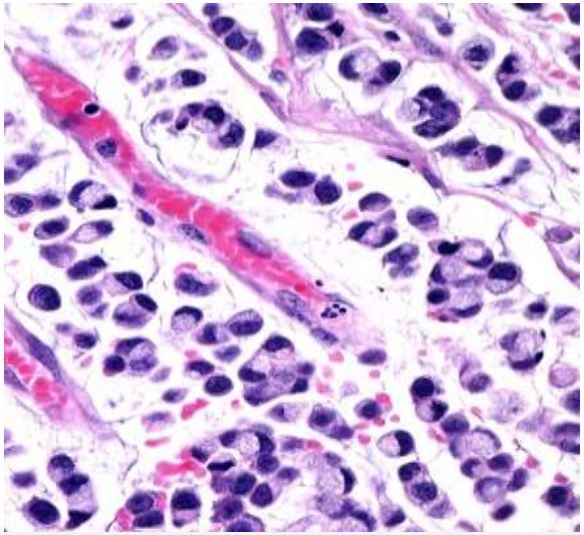
Colorectal adenocarcinoma



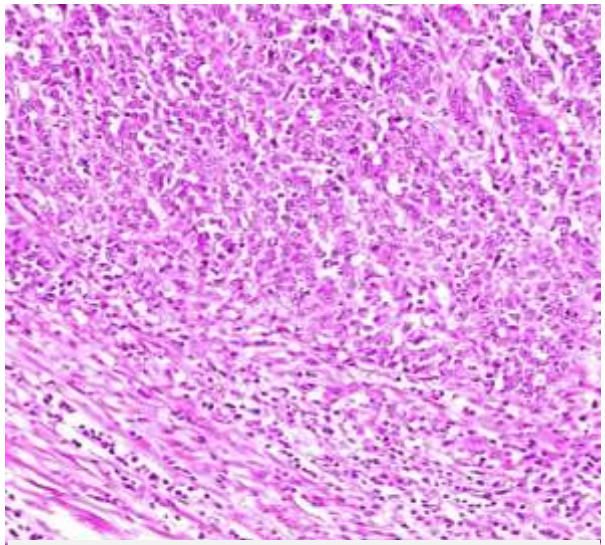
Adenocarcinoma NOS



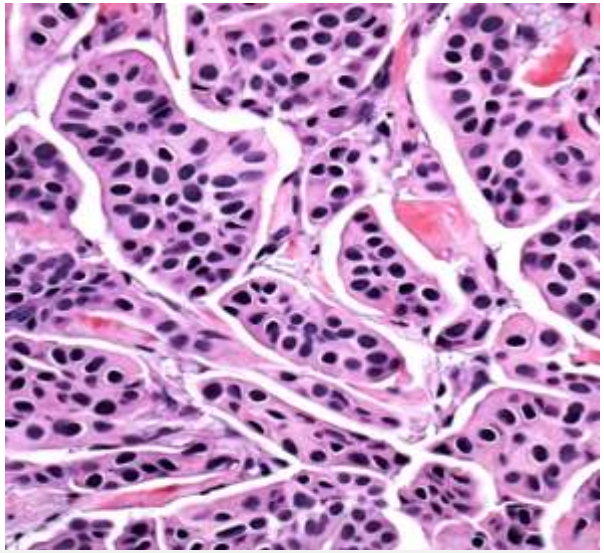
Mucinous



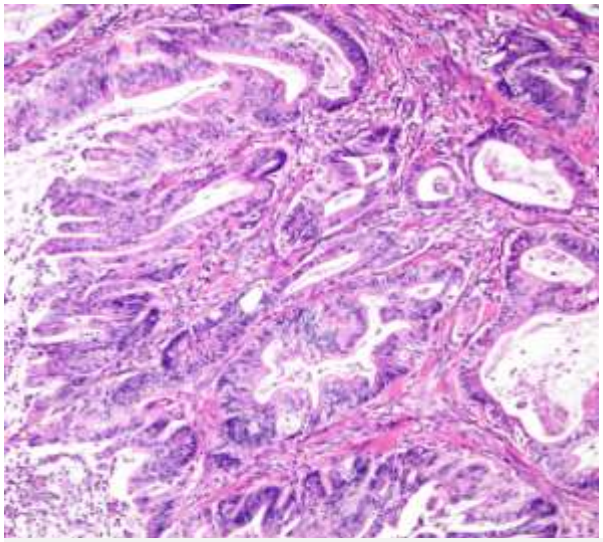
Signet ring cell



Medullary



Micropapillary



Serrated

IHC Markers for Colorectal Cancer Diagnosis and Prognosis	
CK20 and CK7	Most colorectal cancers are CK7-negative and CK20-positive, making this combination an excellent biomarker
CDX2	Marker of enteric differentiation, though not entirely colorectal specific, CDX2 is positive in over 90% of colorectal adenocarcinomas
SATB2:	Highly specific for colorectal carcinoma, positive in a significant portion of cases, making it a valuable tool for diagnosis
Villin	Often expressed in both colonic and appendiceal adenocarcinoma (brush-border staining pattern)
Cadherin-17	Comparable to SATB2, but with slightly lower specificity

Prognostic factors in colorectal cancers (local, regional and distant factors)	
Depth of invasion	Tumors limited to the submucosa have 5-year survival rates of 95% or more Invasion of the muscularis propria reduces 5-year survival to 70%
Lymphovascular, large vein and perineural invasion	Significant prognostic factors that indicate a higher risk of recurrence and poorer overall survival
Tumor budding	Tumor budding is defined as single infiltrating cells or groups of up to 4 neoplastic cells intimately associated with larger invasive glands
Host immune response	Crohn-like lymphoid reaction or tertiary lymphoid structure (TLS) Tumor-infiltrating lymphocytes
Lymph node metastases	Compromises survival and cases with lymph node metastases receive radiation or chemotherapy
Distant metastases	Metastases to liver, lung, bone, brain, other sites limit survival <15% of patients with tumors at this stage are alive 5 years after diagnosis

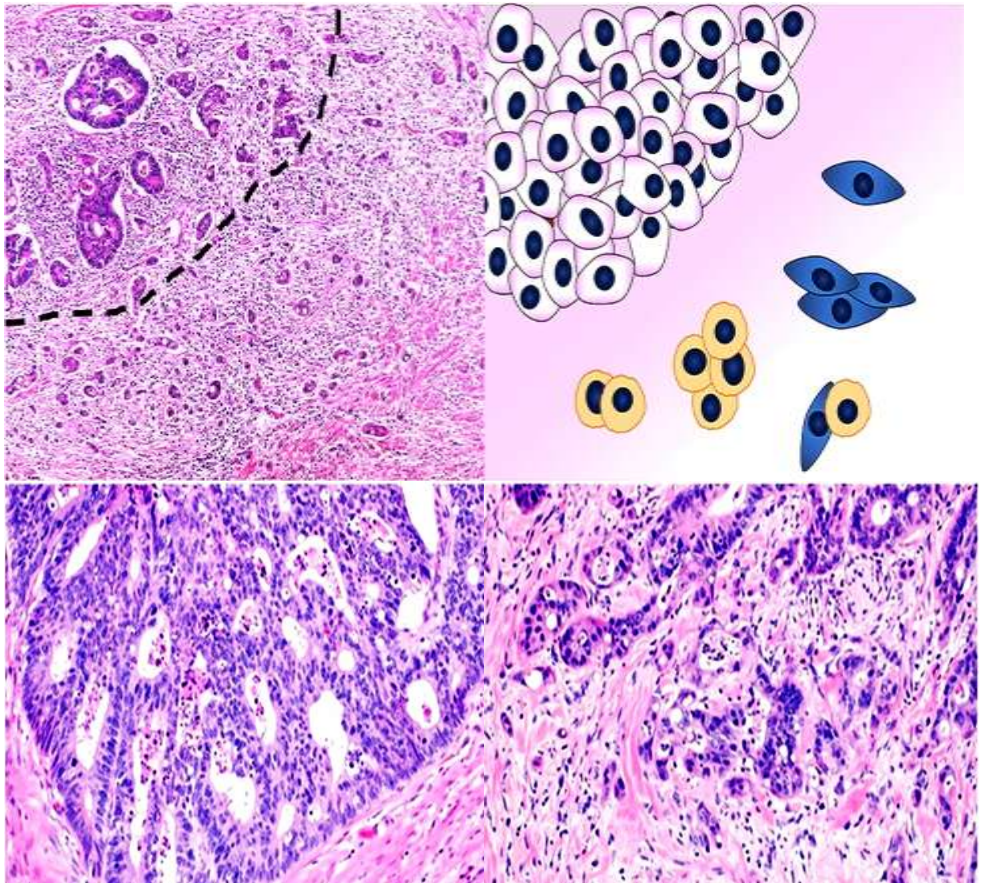
Tumor budding

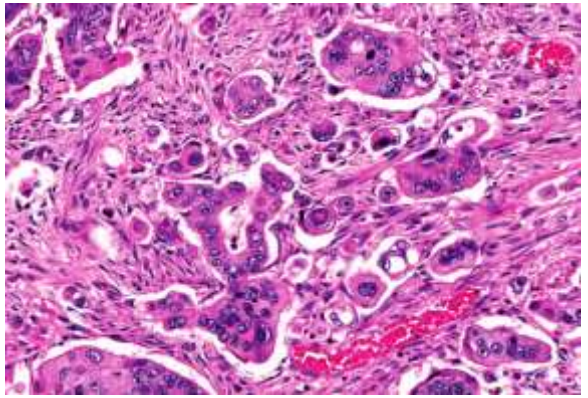
Tumor budding is defined as **single infiltrating cells or groups of up to 4 neoplastic cells** intimately associated with larger invasive glands

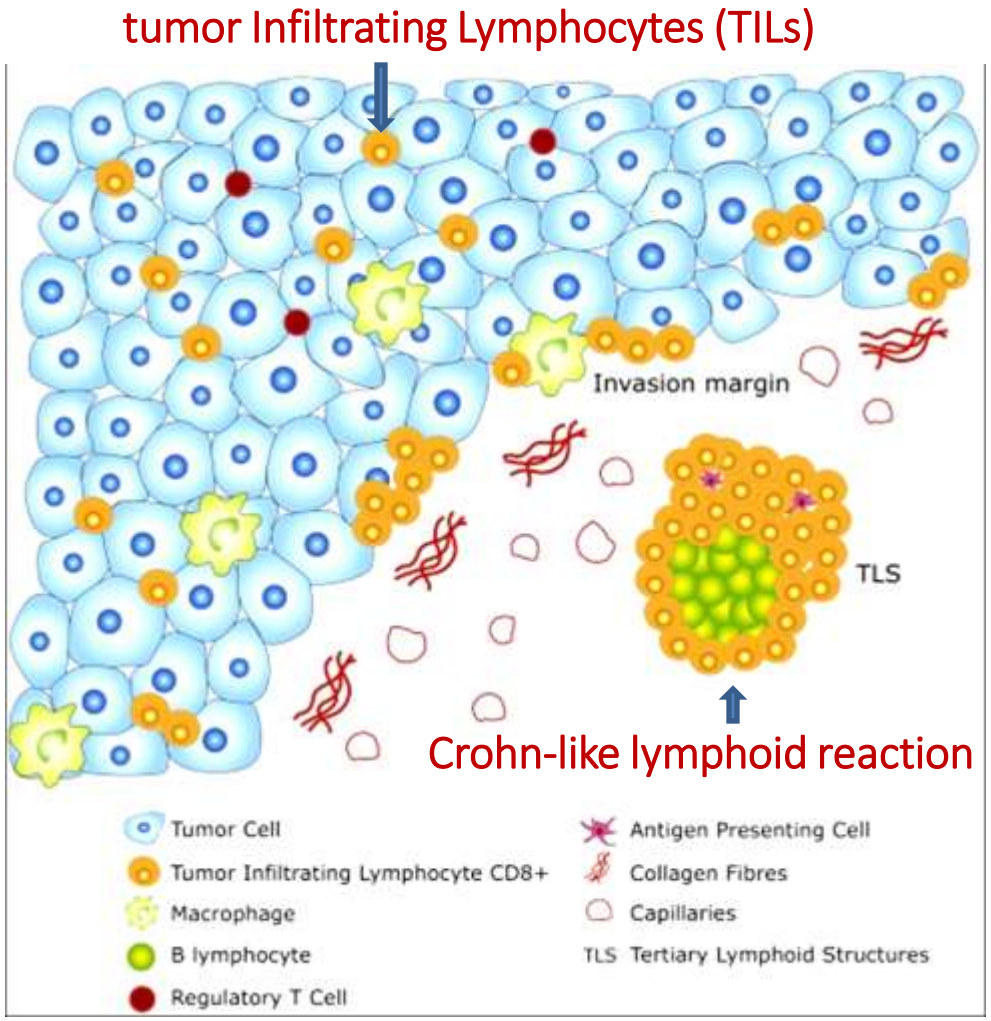
Tumor budding is **an independent prognostic factor, associated with tumor progression and adverse outcome**

Tumor budding is **graded** by counting the number **of individual cells and small clusters per 20x** objective in **hot spots areas** (advancing tumor edge) as

- **Low (0-4 buds)**
- **Intermediate (5-9 buds)**
- **High (≥10 buds)**







Host immune response

Independently associated with **improved outcome**, regardless of mismatch repair status

Crohn-like lymphoid reaction or tertiary lymphoid structure (TLS) (lymphoid follicles with germinal centres at the advancing tumor edge)

Tumor-infiltrating lymphocytes (TILs) with lymphocytes that directly oppose or surround tumor cells

Lymphoid structures

Primary lymphoid structures

Bone marrow and thymus

Generation and maturation of lymphocytes

Secondary lymphoid structures

Lymph nodes, tonsils, spleen, Peyer's patches and mucosa associated lymphoid tissue (MALT)

Located throughout the body

Filter lymph and blood for antigens

Tertiary lymphoid structures

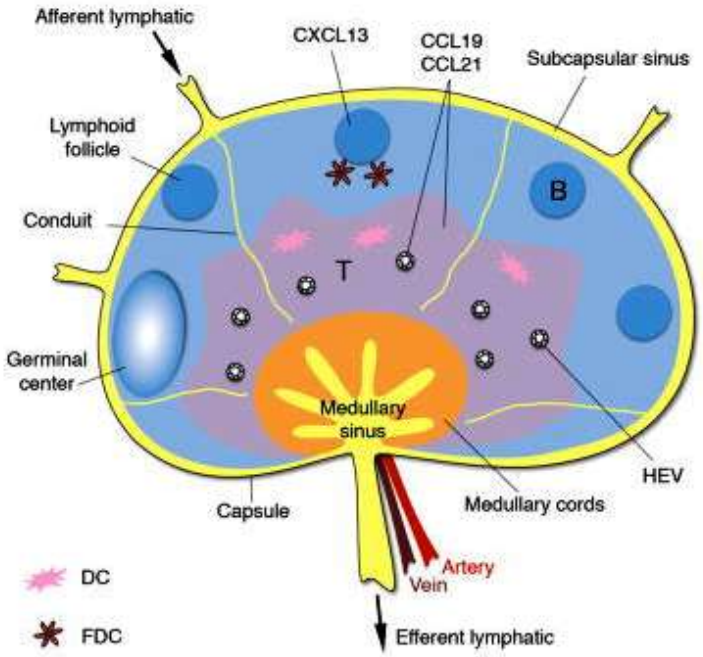
Non-lymphoid tissues

Form in response to infection or other immune reactions (directly exposed to antigenic stimulation)

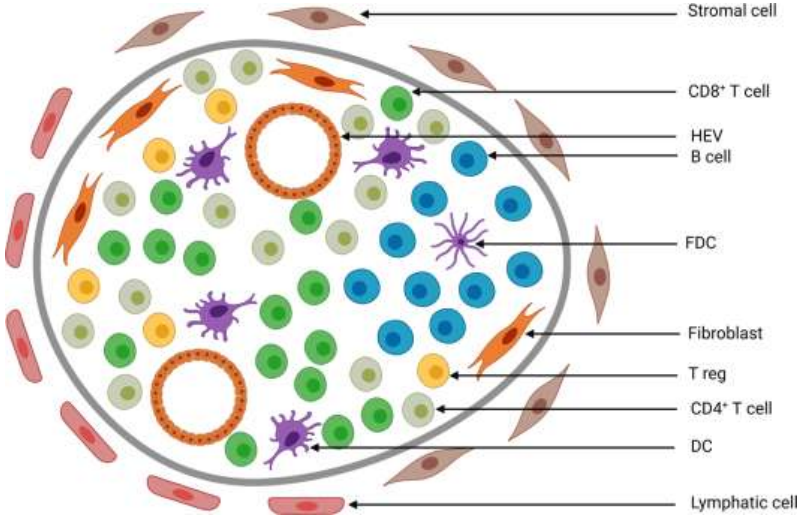
Mimic the structure of secondary lymphoid organs

Lack capsule

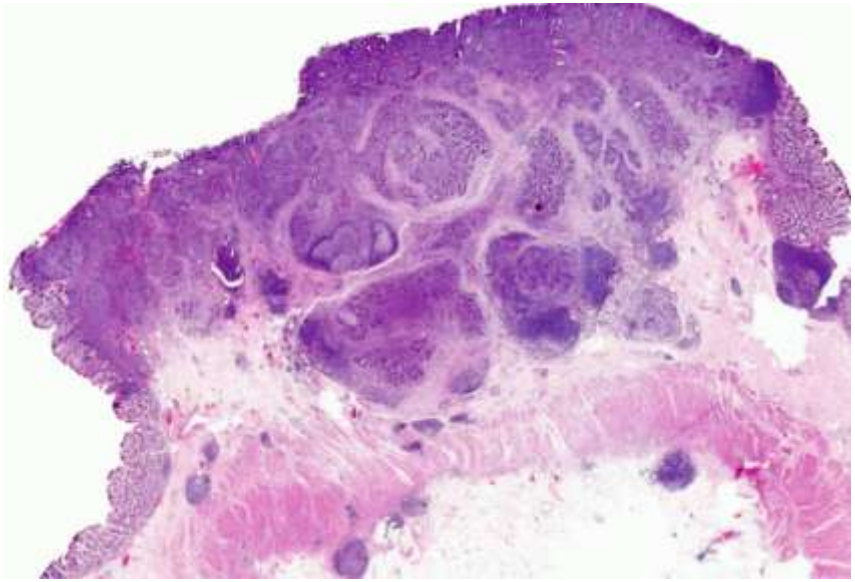
More effective at generating immune responses than secondary lymphoid organs

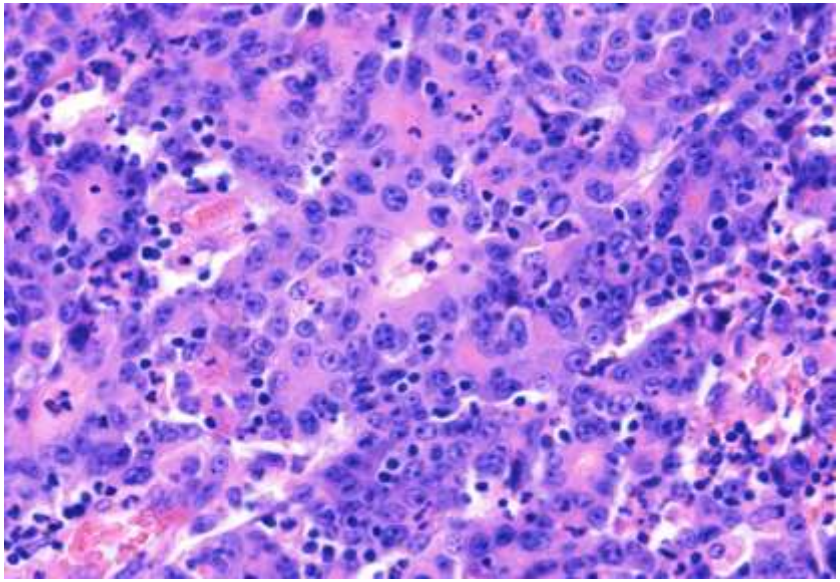


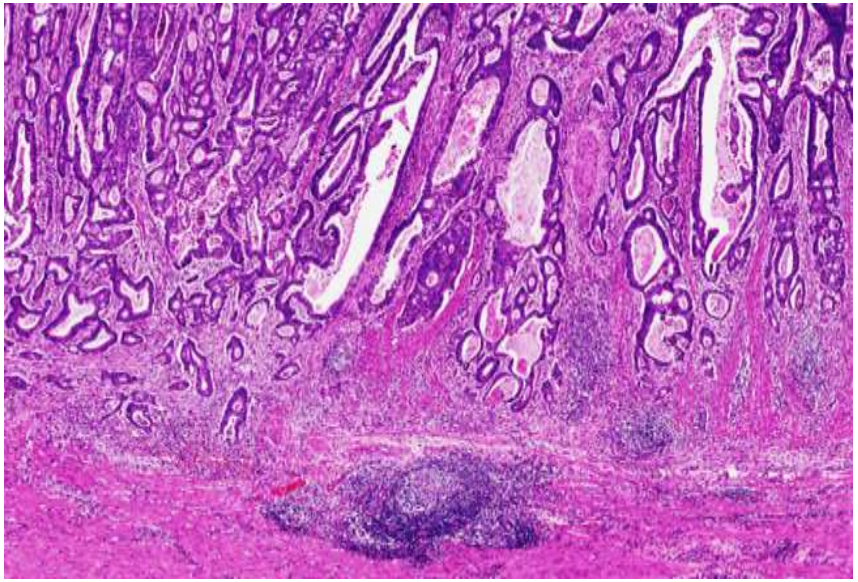
Secondary lymphoid structure (lymph node)



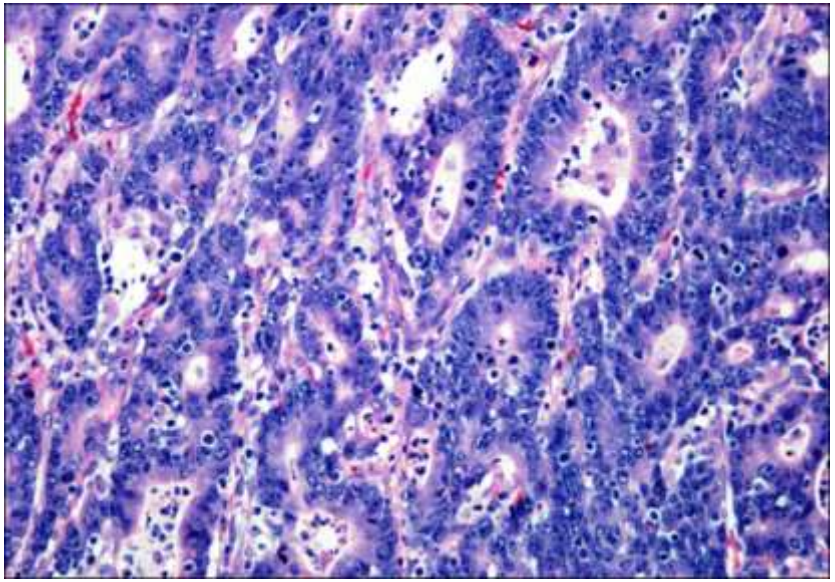
Tertiary lymphoid structure (lymph node)







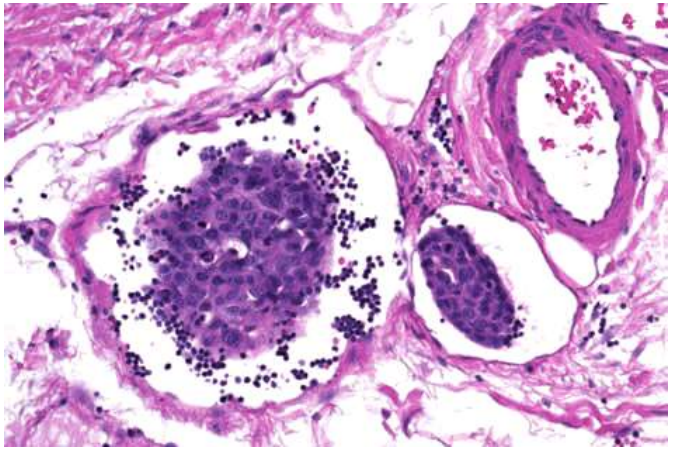
Crohn-like lymphoid reaction (CLR)



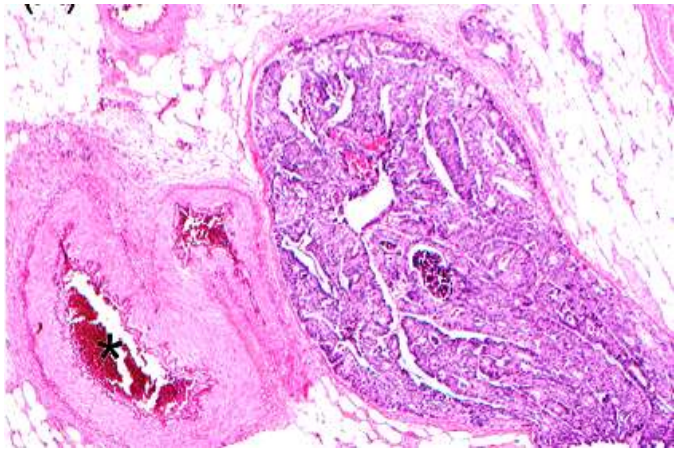
Tumor Infiltrating lymphocytes (TILs)

Prognostic features

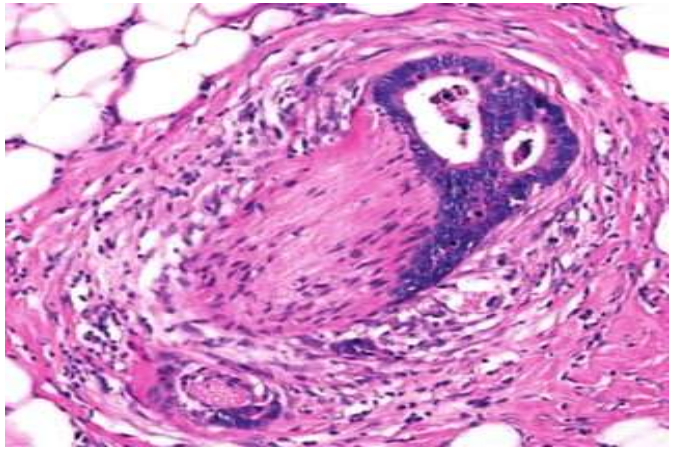
- Lymphovascular space invasion



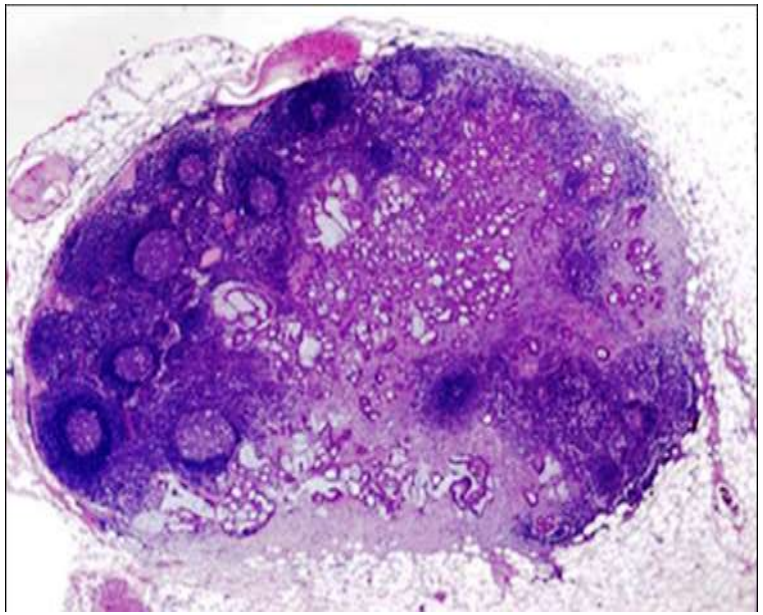
- Large vein invasion



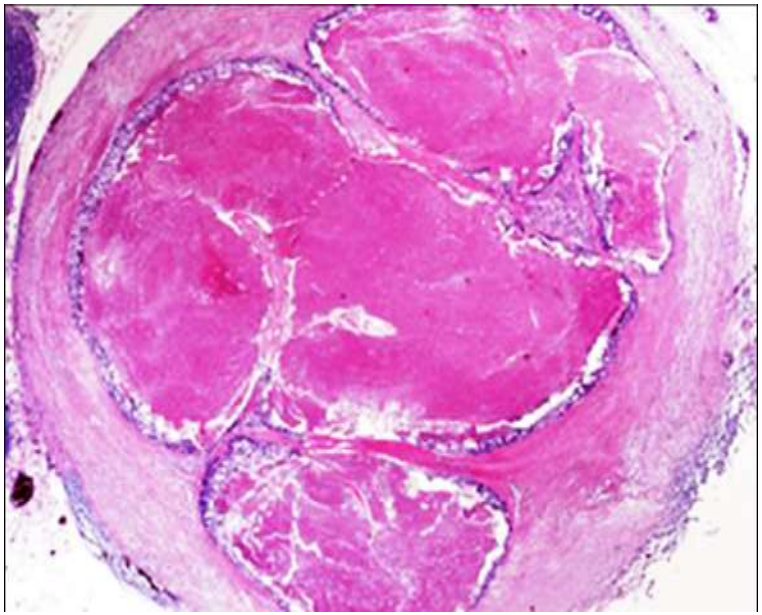
- Perineural Invasion

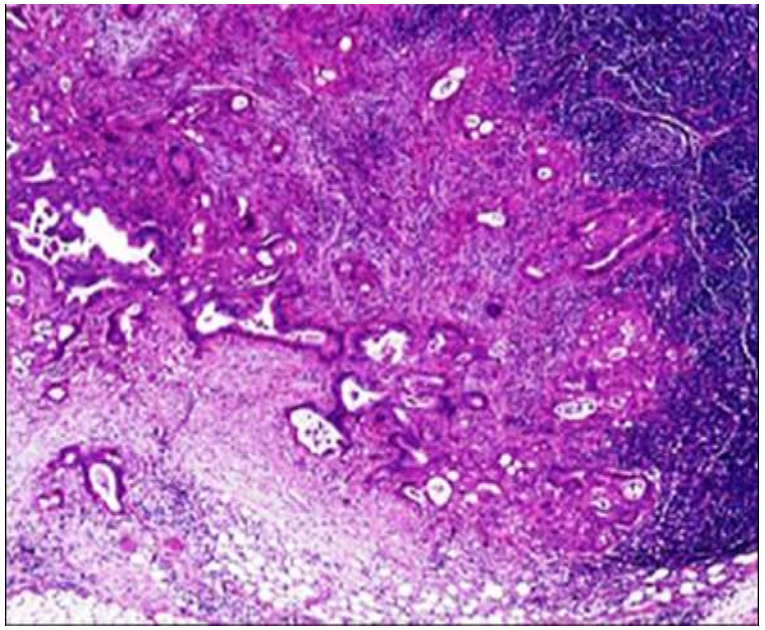


Lymph node with metastatic carcinoma

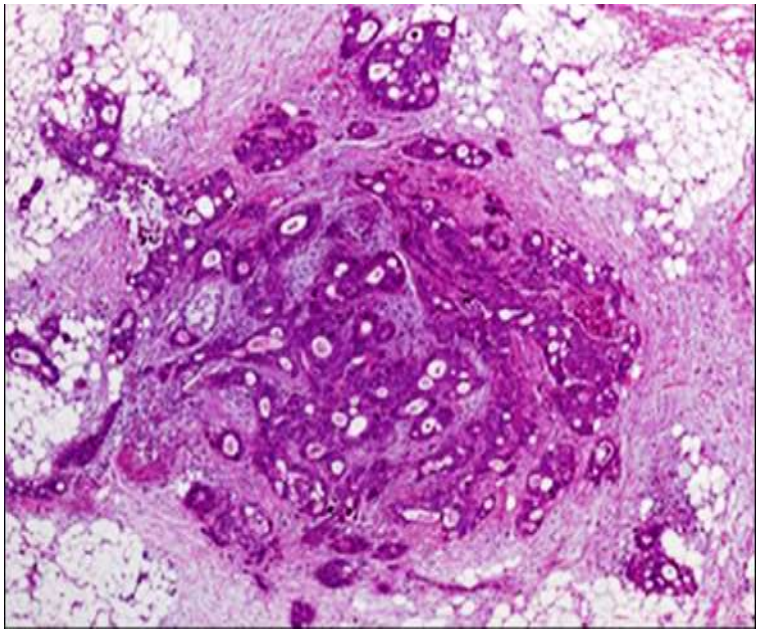


Lymph node with metastatic carcinoma

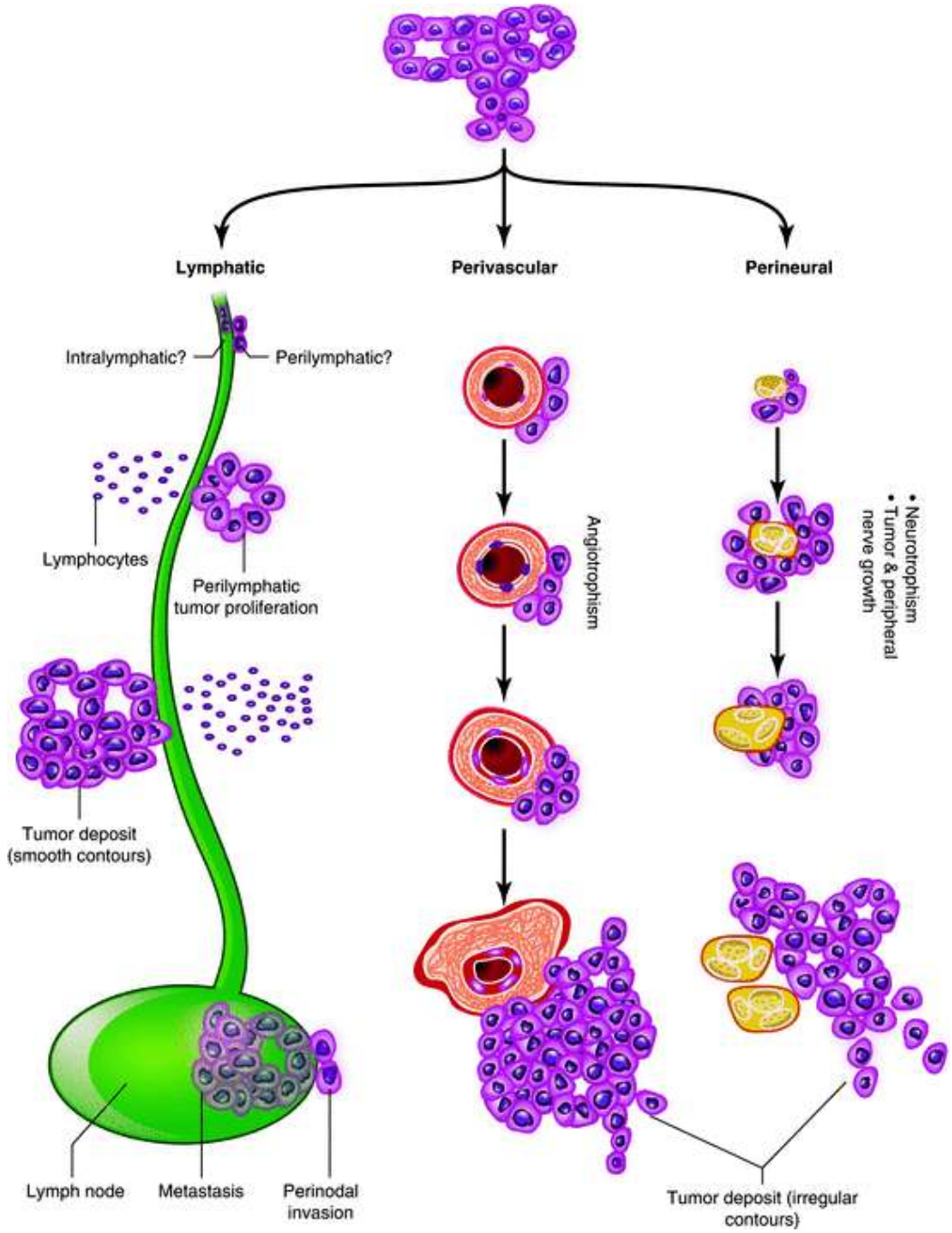




Lymph node with metastatic carcinoma



Tumor deposit



Tumor deposits (TDs)

Collections of cells in the fat around the colon or rectum

Sign of poor prognosis and are associated with a higher risk of recurrence

What are tumor deposits (TDs)?

Collections of cancer cells in the pericolic or perirectal fat

Lymphovascular drainage area of the tumor

Not in lymph nodes

Distant from the tumor invasion front (discontinuous with the main tumor)

No recognizable residual lymph node tissue

How are TDs?

Only included in the TNM staging when there is no lymph node metastasis

Only included in stage III pN1c tumors

What are TDs associated with?

TDs often seen in large tumors, advanced stage, poor differentiation, PNI and LVI

What is the impact of TDs?

Independent poor prognostic factor

Higher risk of local recurrence and peritoneal disease

Pathways to colorectal cancer

Pathway	Frequency	Examples	Molecular pathway TCAG
Conventional Pathway 1928	70%-75%	Adenoma-carcinoma APC gene mutations	Chromosomal instability (CIN) APC KRAS, P53
Microsatellite instability pathway (MSI) 1993	10%-15%	MMR genes inactivation Sporadic (HNPCC) Germ-line mutation (Lynch syndrome)	MMR (MLH1, PMS2, MSH2, MSH6)
Serrated neoplastic Pathway 1996	10%-15%	MSI BRAF MLH1 methylation	CIMP (CpG island methylator phenotype) MSI, BRAF, MLH1 methylation

Chromosomal instability pathway
"Conventional Pathway"

- Accounts for **75% of CRCs**
- Molecular counterpart to the **adenoma-carcinoma sequence**
- Adenomas develop as a result of **APC gene inactivation**
- **Sporadic adenomas** account for 99% of the cases
- **Syndromic germline** APC mutations (familial adenomatous polyposis) account the remaining 1%
- **APC** is the main affected gene
- APC mutations lead to **accumulation of β-catenin** which allows overexpression of growth promoters like **MYC and Cyclin D1**
- **Activating mutations in KRAS and silencing of p53 and other tumor suppressor genes**
- **Increased expression of telomerase** as lesions become more advanced

Microsatellite instability (MSI) pathway
Mismatch Repair Gene (MMR) mutations (defects)

- Accounts for 15% of CRCs
- Inactivation of mismatch repair genes (MLH1, MSH2, MSH6 and PMS2)
- Sporadic (methylation of MLH1) 12%-15%
- Germline mutations in MMR genes (Lynch syndrome) 3%-5%
- Predilection for **proximal colon of older patients**, particularly women and show **BRAF V600E mutations in 50%** of the cases
- Cancers are often **medullary, solid areas, mucinous or signet-ring cells**
- Most MSI CRCs show **host immune responses** and display **tumor-infiltrating lymphocytes (TILs) or a Crohn-like lymphoid reaction**

Microsatellite instability (MSI) pathway

Mismatch repair (MMR) deficiency can be assessed
- **PCR** for MSI
- **IHC** for MMR protein (MLH1, PMS2, MSH2 and MSH6)
- **NGS** for MMR genes mutations and mutational burden

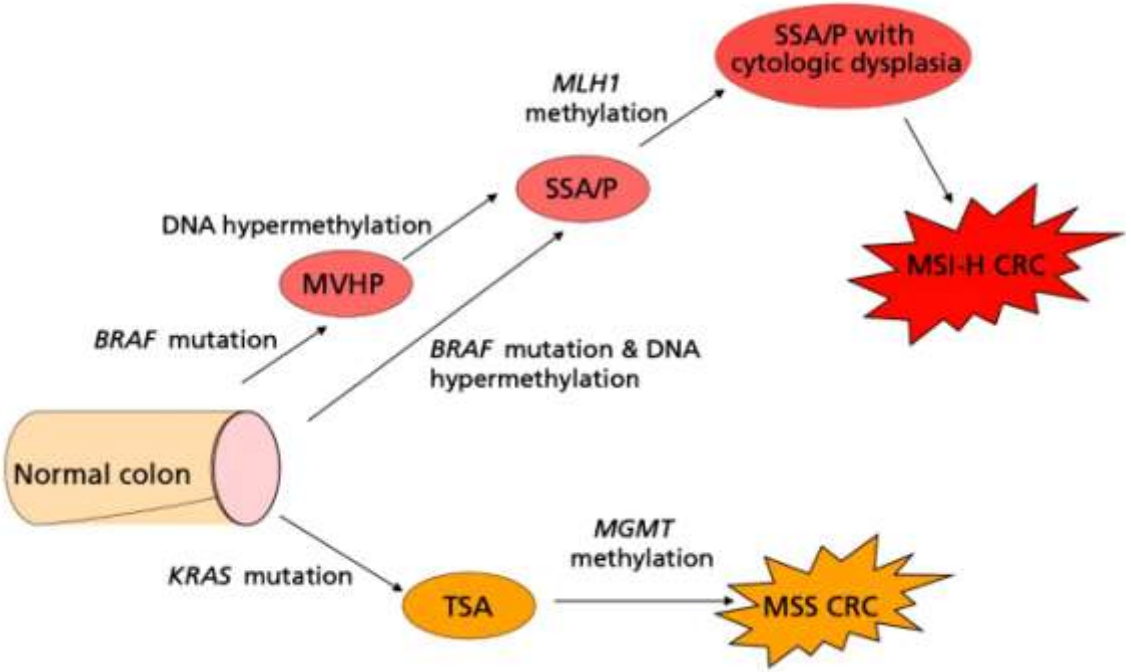
MMR deficient tumors are **MSI-H**

MMR proficient tumors are **MSS**

Tumors with instability at one locus are classified as **indeterminate**

The serrated neoplastic pathway

- Accounts for 10%-15% of CRCs
- Several routes and overlapping mechanisms (BRAF, KRAS, DNA methylation) from normal to serrated polyps to cancer (MSI and MSS tumors) involved
- Some progress through an intermediate dysplastic step (SSP with dysplasia) to MMR deficient adenocarcinomas with BRAF mutations and are of CIMP phenotype



CpG Island Methylator Phenotype (CIMP)

CIMP tumors, comprising 15% of colorectal cancers

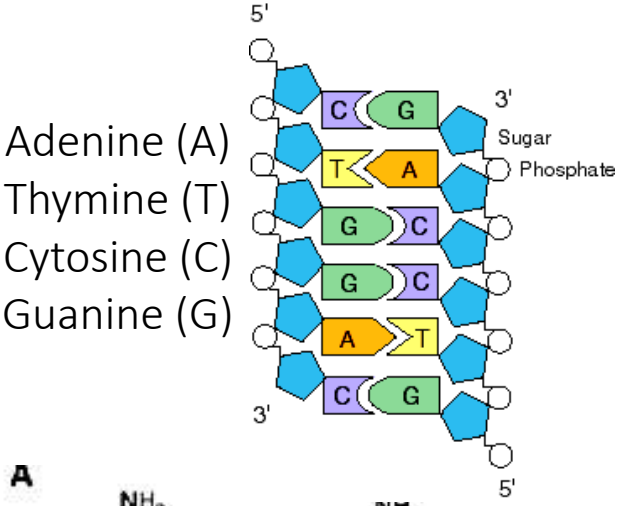
Associated with female sex, older age, right colon location, and BRAF mutations

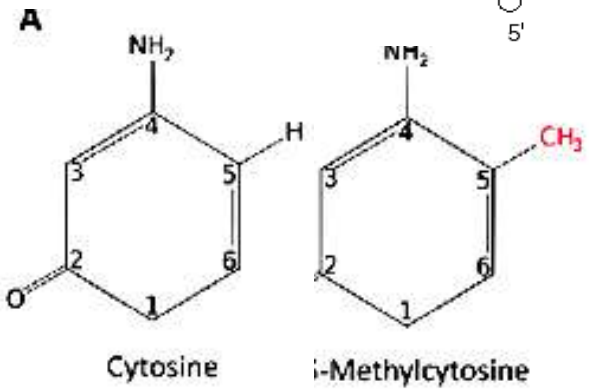
CpG islands are **regions with high concentration of cytosine-guanine (C-G) pairs**

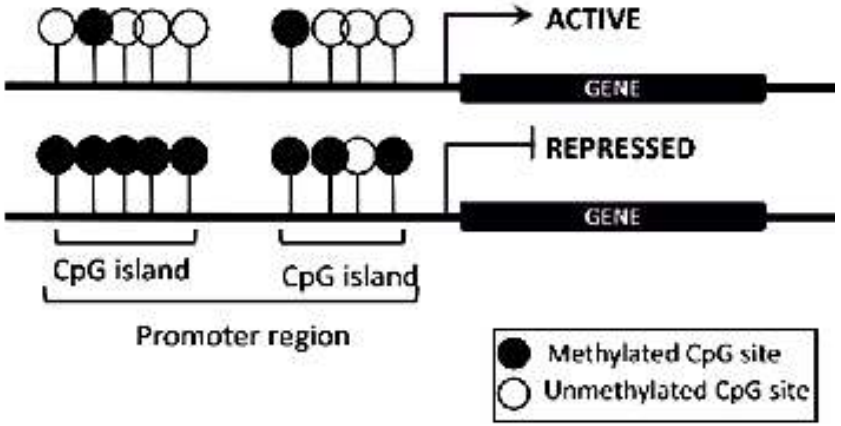
Found in many gene promoters regions

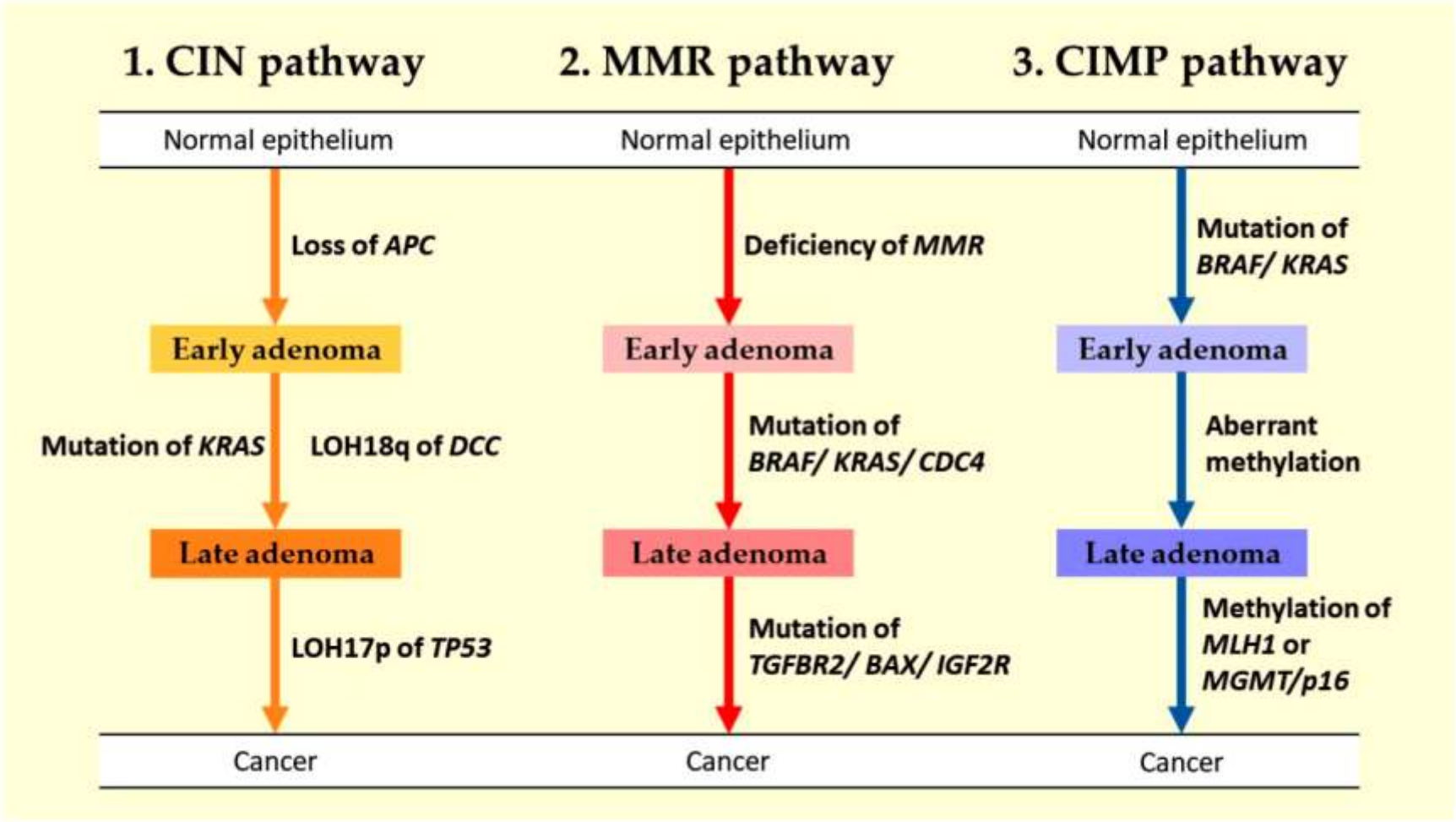
Normal CpG islands are **not methylated**

Methylation of CpG island can inactivate gene expression

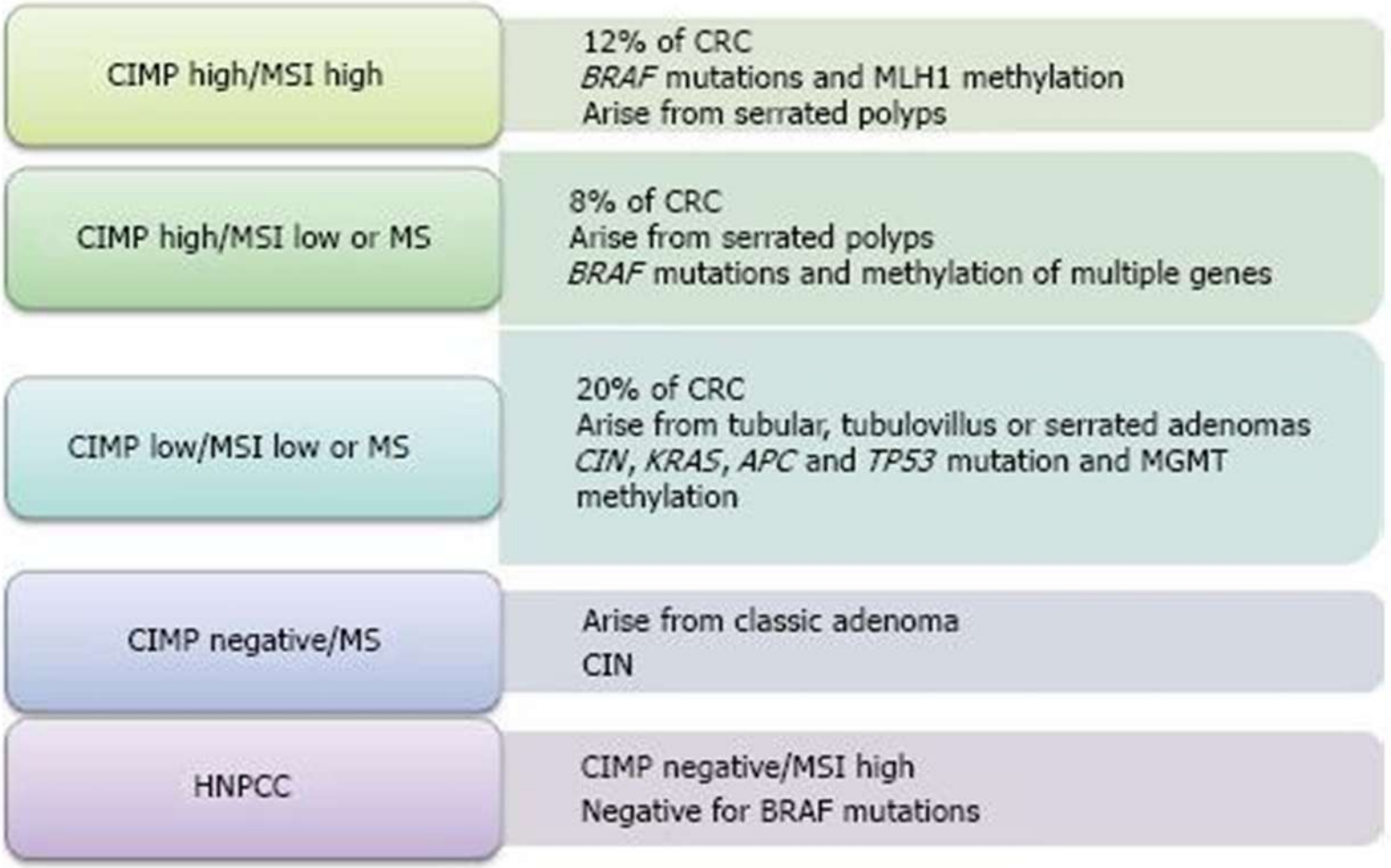







1. CIN pathway
2. MMR pathway
3. CIMP pathway
Normal epithelium
Normal epithelium
Normal epithelium
Loss of APC
Deficiency of MMR
Mutation of BRAF/ KRAS
Early adenoma
Early adenoma
Early adenoma
Mutation of KRAS
LOH18q of DCC
Mutation of BRAF/ KRAS/ CDC4
Aberrant methylation
Late adenoma
Late adenoma
Late adenoma
LOH17p of TP53
Mutation of TGFBR2/ BAX/ IGF2R
Methylation of MLH1 or MGMT/p16
Cancer
Cancer
Cancer

CIMP (CpG island methylator phenotype) and MSI

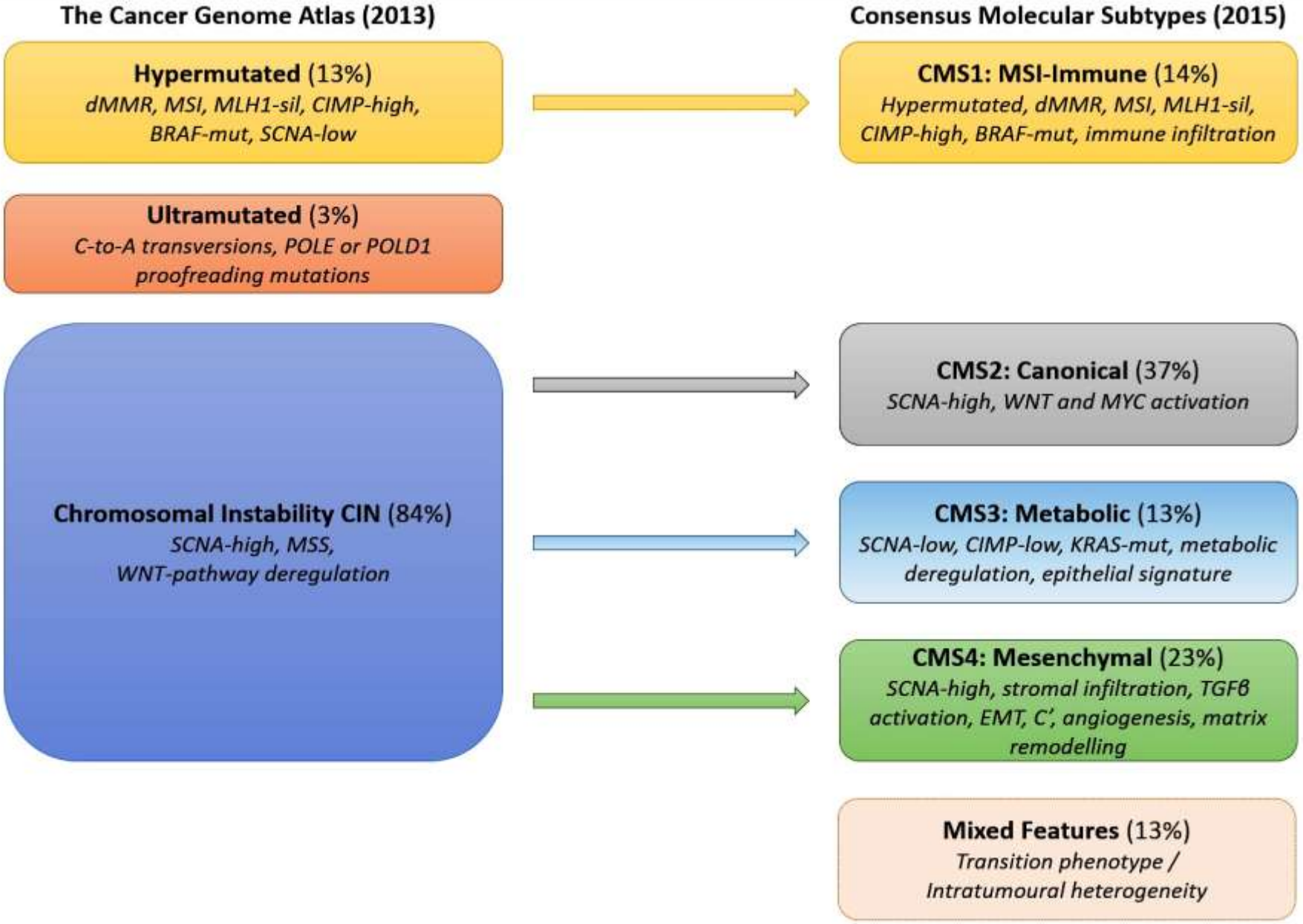

CIMP high/MSI high
12% of CRC
BRAF mutations and MLH1 methylation
Arise from serrated polyps
CIMP high/MSI low or MS
8% of CRC
Arise from serrated polyps
BRAF mutations and methylation of multiple genes
CIMP low/MSI low or MS
20% of CRC
Arise from tubular, tubulovillus or serrated adenomas
CIN, *KRAS*, *APC* and *TP53* mutation and MGMT methylation
CIMP negative/MS
Arise from classic adenoma
CIN
HNPCC
CIMP negative/MSI high
Negative for BRAF mutations

Relationship between CIMP and MSI

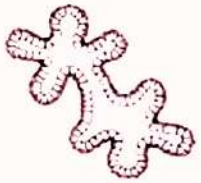
80% of CIMP-positive tumors are MSI-H , especially in sporadic (non-hereditary) colorectal cancers but there are major differences between them

CIMP-positive tumors	MSI-high tumors
CIMP-positive tumors are **more aggressive** and are generally considered **"bad"**	MSI-high tumors are **less aggressive** in early-stage CRC and are considered **"good"** **Do not respond to 5-fluorouracil** treatment **Better response to immunotherapy**
Extensive DNA methylation at CpG islands, which can **silence tumor suppressor genes**, leading to **uncontrolled cell growth and tumor progression**	**Deficient DNA mismatch repair system**, causing numerous mutations **(high TMB)** that can **trigger an immune response**
More common in females Occur in proximal colon Poor differentiation with mucinous component Higher risk of recurrence, especially when combined with MSI-H BRAF mutations No benefit from immunotherapy	Found in older female patients Occur in proximal colon Poorly differentiated with mucinous/signet ring cell morphology High TILs, a "Crohn-like" lymphocytic reaction Benefit from immune checkpoint inhibitors

Characteristics of serrated carcinomas	
BRAF mutations	BRAF V600E mutation is an **early event** in the serrated neoplasms
KRAS mutations	Less common than BRAF mutations, occurs mainly in **traditional serrated adenomas (TSA)**
CIMP	**Hallmark of serrated neoplasia** (methylation in the promoter regions, silences expression of tumor suppressor gene which contributes to tumor progression)
Histology	Serrated polyps have a characteristic **sawtooth appearance on microscopic examination**
Location	**SSAs are found in the proximal colon** **TSAs occur in the left colon**
Clinical presentation	May be **asymptomatic** and are often detected during routine colonoscopy due to their subtle appearance Can cause **bleeding, anemia, etc**


The Cancer Genome Atlas (2013)
Consensus Molecular Subtypes (2015)
Hypermutated (13%)
dMMR, MSI, MLH1-sil, CIMP-high, BRAF-mut, SCNA-low
CMS1: MSI-Immune (14%)
Hypermutated, dMMR, MSI, MLH1-sil, CIMP-high, BRAF-mut, immune infiltration
Ultramutated (3%)
C-to-A transversions, POLE or POLD1 proofreading mutations
Chromosomal Instability CIN (84%)
SCNA-high, MSS, WNT-pathway deregulation
CMS2: Canonical (37%)
SCNA-high, WNT and MYC activation
CMS3: Metabolic (13%)
SCNA-low, CIMP-low, KRAS-mut, metabolic deregulation, epithelial signature
CMS4: Mesenchymal (23%)
SCNA-high, stromal infiltration, TGFβ activation, EMT, C', angiogenesis, matrix remodelling
Mixed Features (13%)
Transition phenotype / Intratumoural heterogeneity

Consensus Molecular Subtype of CRC (2015)

	CMS1	CMS2	CMS3	CMS4
Alternate Name	MSI immune	Canonical	Metabolic	Mesenchymal
Incidence	14%	37%	13%	23%
Molecular Features	MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
Mutations	*BRAF*		*KRAS*	
Signatures	Immune infiltration and activation	*WNT* and *MYC* activation	Metabolic deregulation	Stromal infiltration, *TGF-β* activation, angiogenesis
Clinical Features	Worse survival after relapse			Worse relapse-free and overall survival
Potential Precursor Lesions	 Serrated	Tubular adenoma	Uncertain (Tubulovillous adenoma with serrated features)	Serrated

SCNA = Somatic Copy Number Alteration; CIMP = CpG island methylator phenotype; TGFβ = Transforming Growth Factor β)

Limitations and possible benefits of the CMS classification of colorectal cancer (CRC)

Better patient stratification (treatment selection and prognosis prediction)

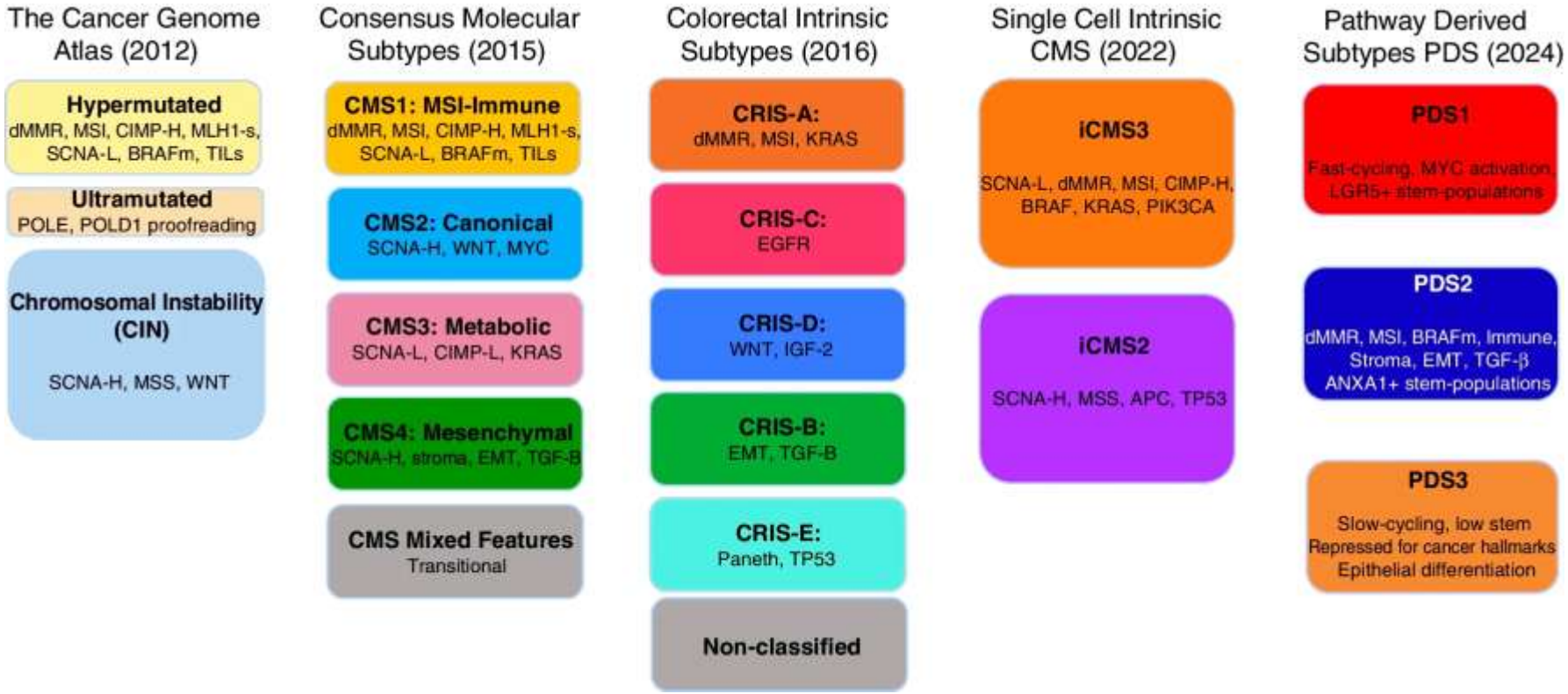
Molecular stratification by capturing **molecular heterogeneity**

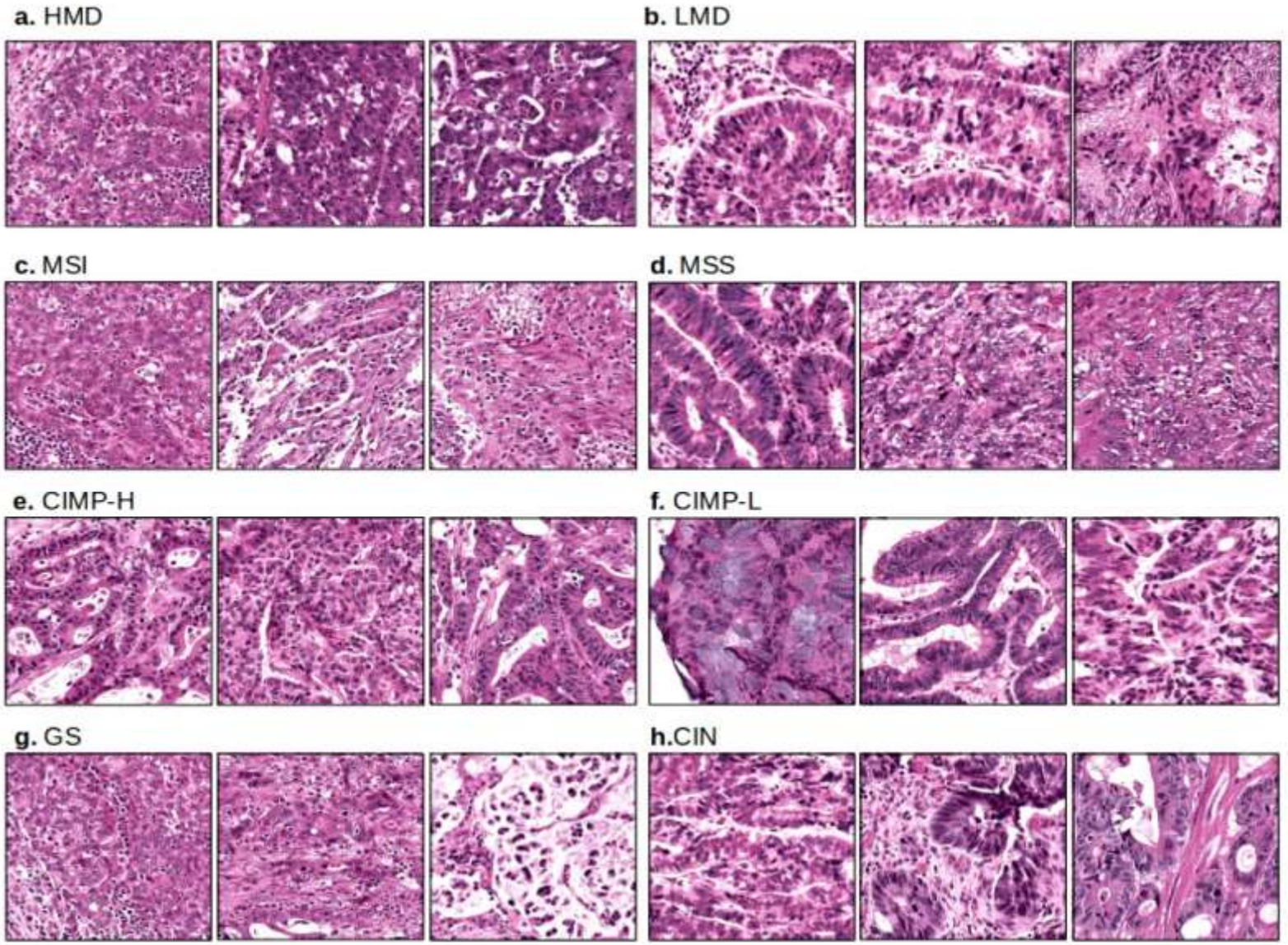
Molecular profile may allow to better predictor survival

Targeted therapy potential based on based on the molecular pathways active in each subtype

Informed treatment decisions (choosing adjuvant chemotherapy or considering targeted therapies based on the identified subtype)

Summary of new “molecular” classifications of colorectal cancers





Microsatellite instability (MSI), Chromosomal Instability (CIN), CpG Island Methylator Phenotype (CIMP), High Mutation Density (HMD), Genomically Stable (GS)

Neoadjuvantly treated carcinomas

Treat locally advanced cancers to **improve resectability and postsurgical quality of life**

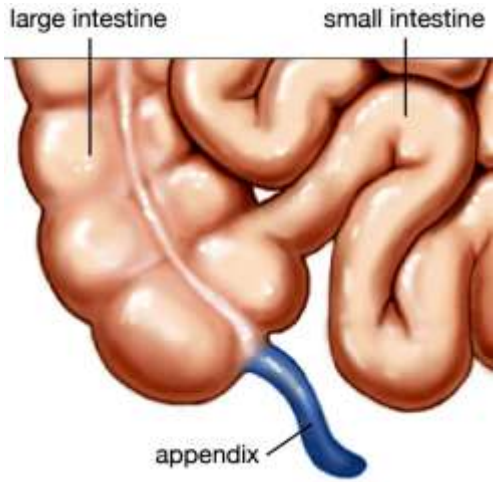
Grading of regression is evaluated (complete response, near-complete response, partial response or poor response)

Therapeutic response (amounts of viable carcinoma, mural fibrosis, dystrophic calcifications and pools of extracellular mucin)

Extent of tumor regression is predictive of prognosis (extensive response is associated with improved disease-free survival compared with those that show little or no response to therapy)

Post neoadjuvant residual carcinoma is **not graded**

- Hyperplastic polyp
- Sessile serrated lesion without dysplasia
- Serrated dysplasia, low grade
- Serrated dysplasia, high grade
- Low grade appendiceal mucinous neoplasm
- High grade appendiceal mucinous neoplasm
- Adenocarcinoma, NOS
  - Mucinous adenocarcinoma
  - Signet ring cell adenocarcinoma
- Carcinoma, undifferentiated, NOS
- Goblet cell adenocarcinoma



- Neuroendocrine tumor, NOS
  - Neuroendocrine tumor, grade 1
  - Neuroendocrine tumor, grade 2
  - Neuroendocrine tumor, grade 3
  - L cell tumor
  - Glucagon-like peptide producing tumor
  - PP / PYY producing tumor
  - Enterochromaffin cell carcinoid
  - Serotonin producing carcinoid
- Neuroendocrine carcinoma, NOS
  - Large cell neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
- Mixed neuroendocrine - nonneuroendocrine neoplasm (MiNEN)

Tumors of the appendix

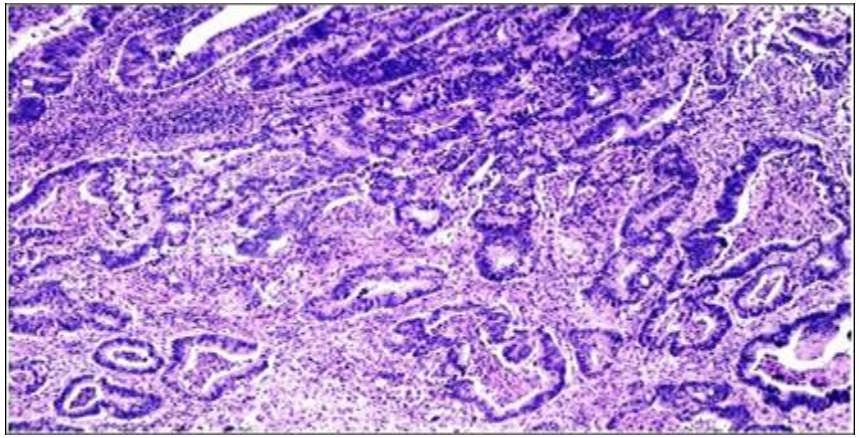
The most common appendiceal tumor is **neuroendocrine neoplasms (carcinoid)**

Mucinous neoplasms, adenomas and adenocarcinomas also occur

Tumors may cause luminal **obstruction** with enlargement

Tumors can **mimic acute appendicitis**

Tumors occur in **older patients**



Tumors of the appendix
without infiltrative invasion

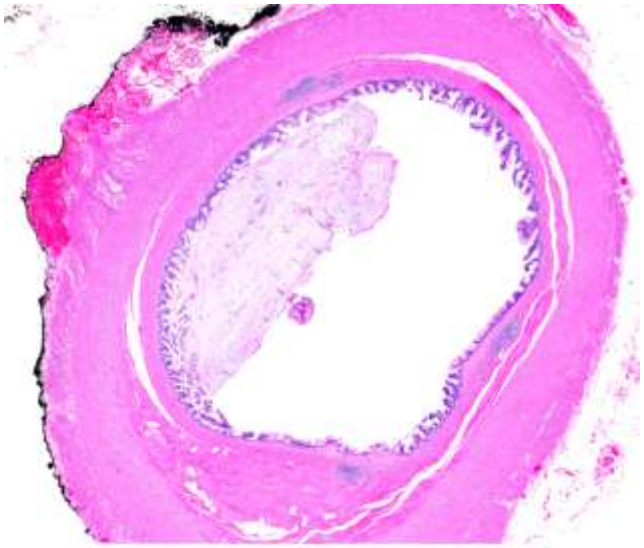
Low-grade appendiceal mucinous neoplasm (LAMN)

High-grade appendiceal mucinous neoplasm (HAMN)

Serrated tumours

Conventional adenoma (rare)

When confined to an intact appendix, patients are generally cured by appendectomy



LAMIN

Adenoma

Appendiceal mucinous neoplasm neoplasms

Replacement of the normal appendiceal mucosa by **filiform (villous) or undulating (scalloped) mucinous epithelium.**

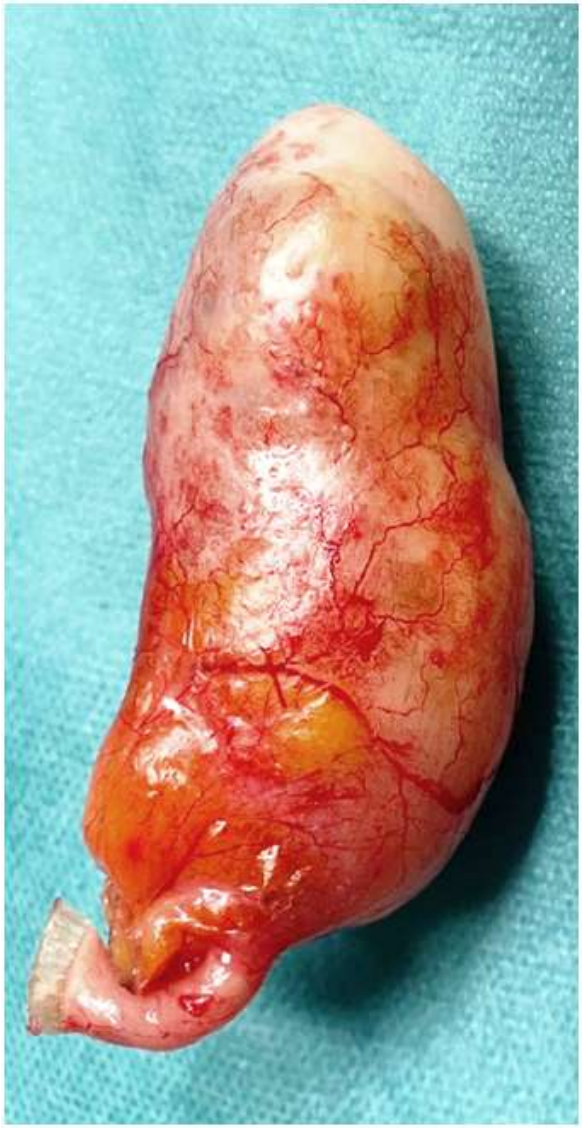
Tumour cells can be **tall with cytoplasmic mucin vacuoles, pseudostratified or attenuated (flattened)**

Cytoplasmic mucin compresses the nucleus

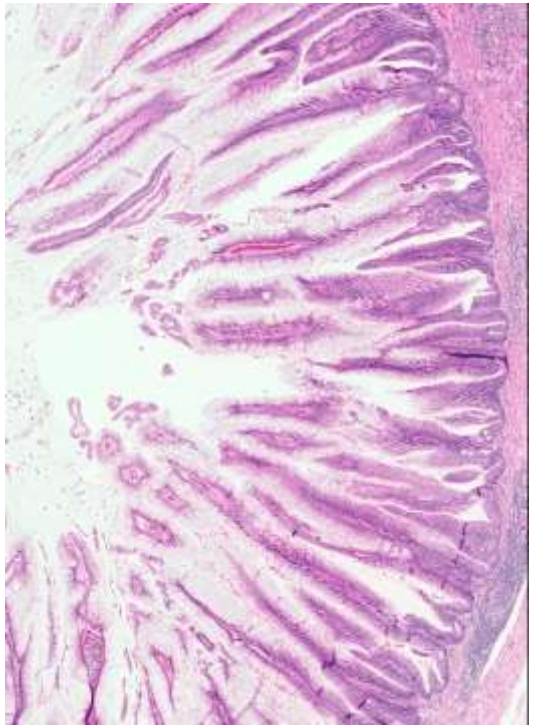
Tumour cells grow on **fibrotic submucosal tissue**.

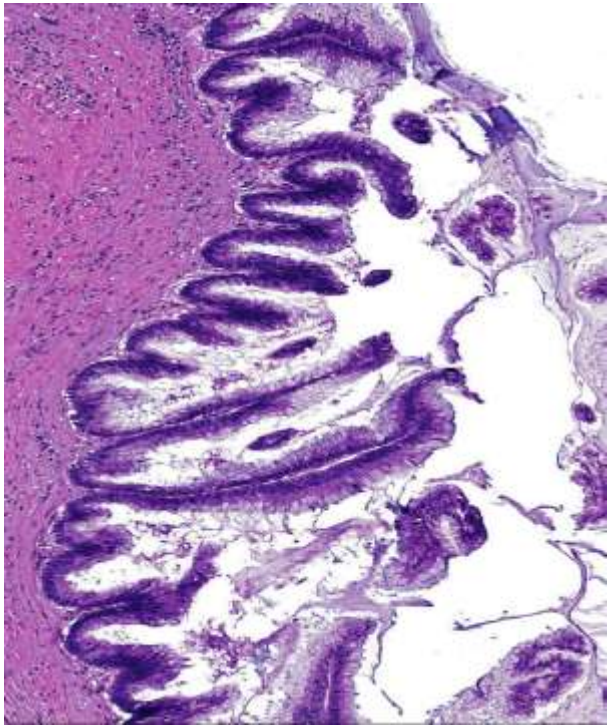
Nuclear atypia can be **low grade (LAMIN) or high grade (HAMIN)**

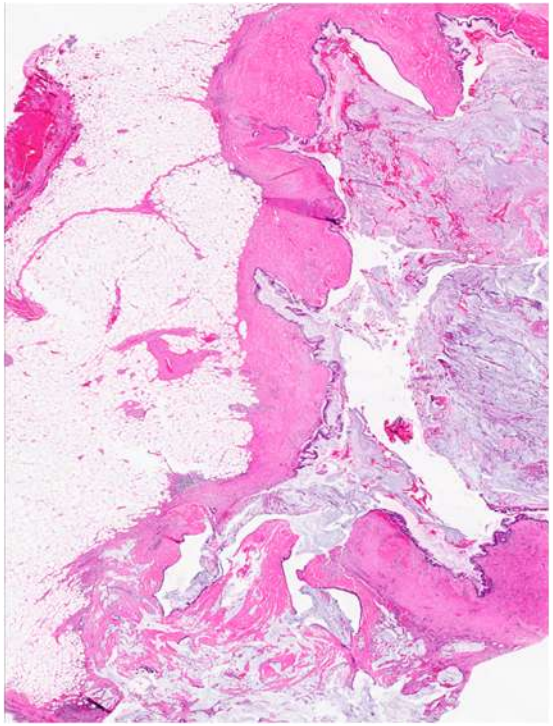
Mucin can dissect through the structures of the appendix and extend to the peritoneal surface or cause rupture of the appendix



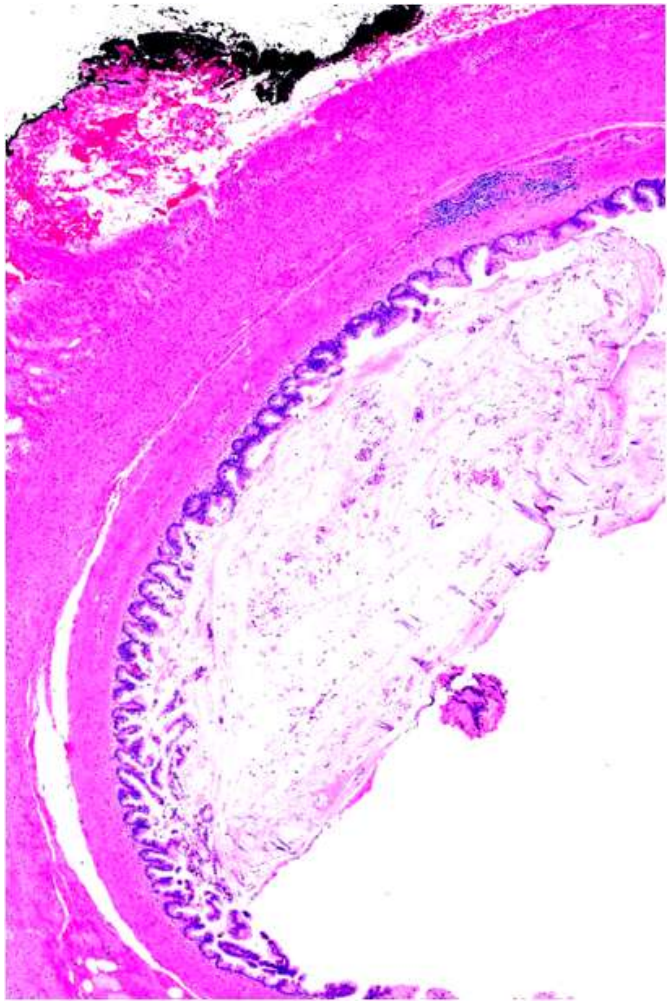
Low-grade appendiceal mucinous neoplasm



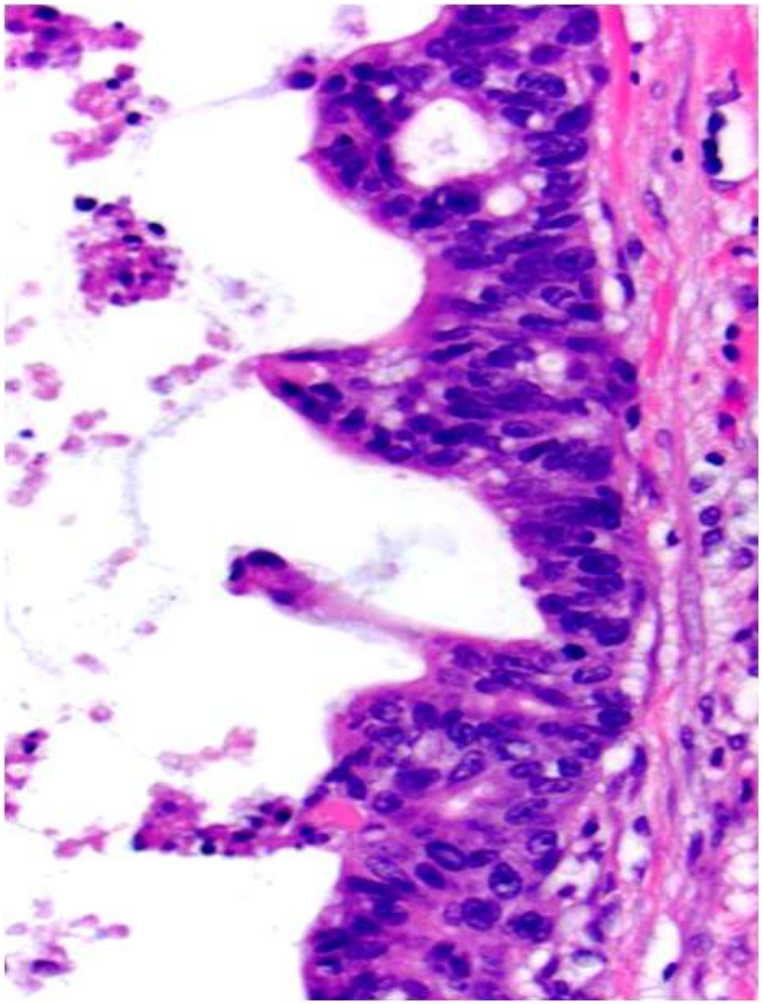




Low-grade appendiceal mucinous neoplasm



High-grade appendiceal mucinous neoplasm



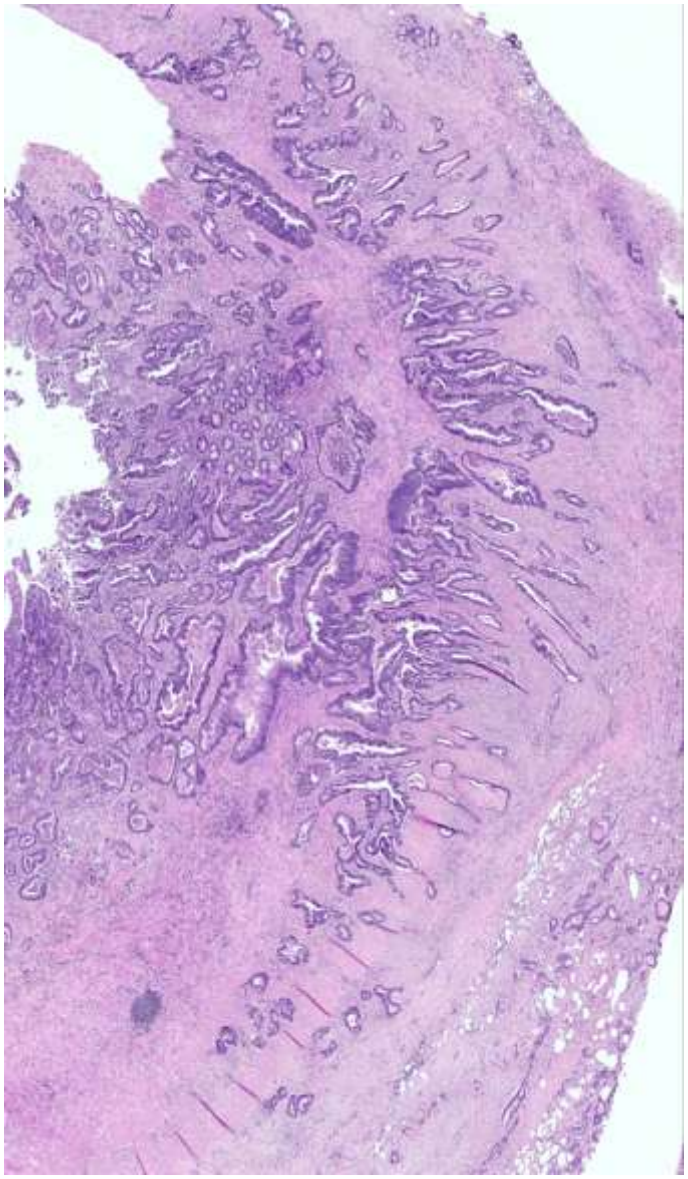
Appendiceal adenocarcinomas

Resemble their colonic counterparts

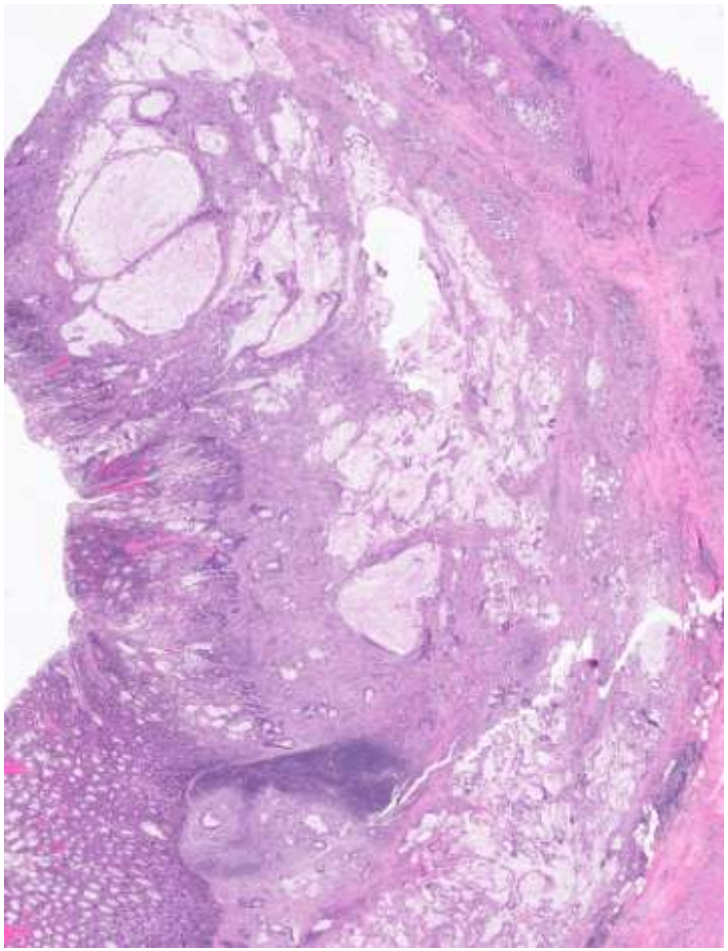
Intestinal-type, mucinous, or signet-ring cell differentiation.

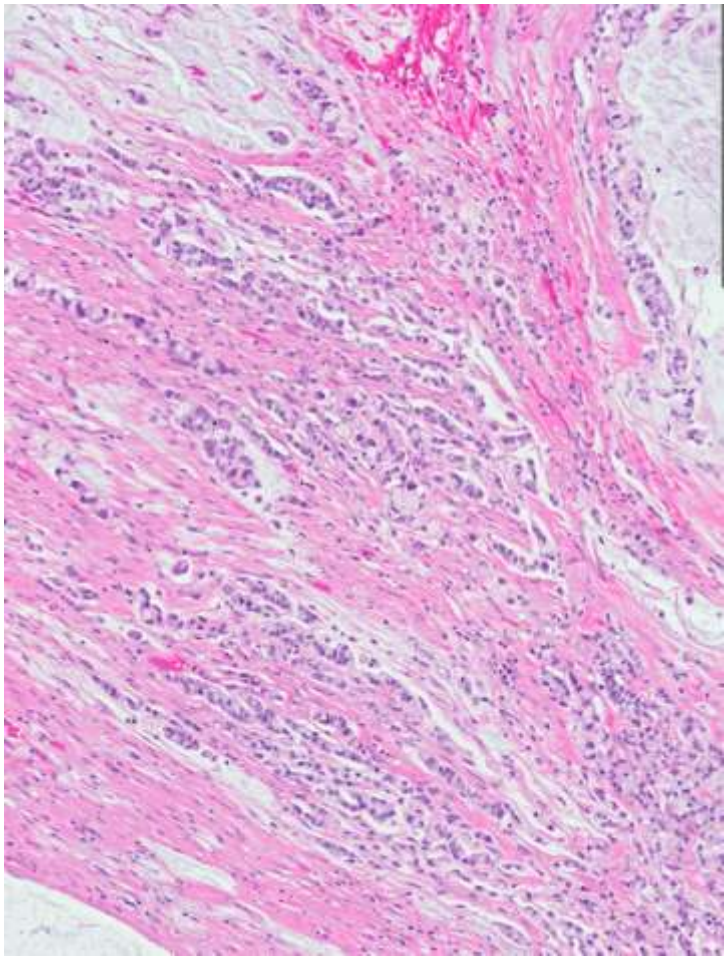
Carcinomas associated **with serrated precursors** feature infiltrative glands with a tubular or serrated appearance and high-grade features accompanied by extracellular mucin

Can cause **pseudomyxoma peritonei** (clinical term that describes massive mucin accumulation in the peritoneal cavity, accompanied by omental caking and gelatinous serosal deposits)



Invasive appendiceal adenocarcinoma

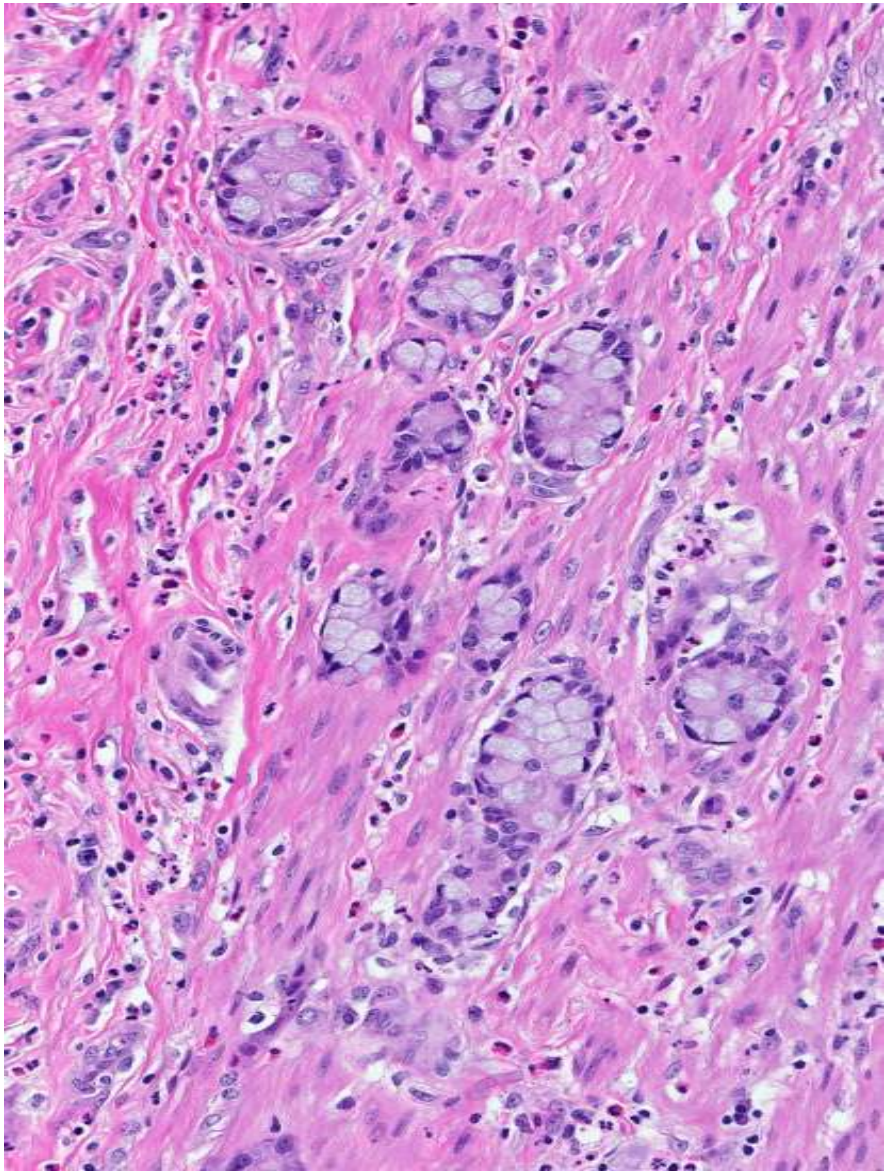




Goblet cell adenocarcinoma (crypt cell carcinoma)
Amphicrine (exocrine and endocrine) tumour

Composed of **goblet-like mucinous cells** and variable numbers of **endocrine cells and Paneth-like cells**

Tumour cells are typically arranged as **tubules resembling intestinal crypts**



Neuroendocrine neoplasms

Seen in **<1% of appendicectomy specimens**

More common among **adults**

Most tumors behave in a **benign manner.**

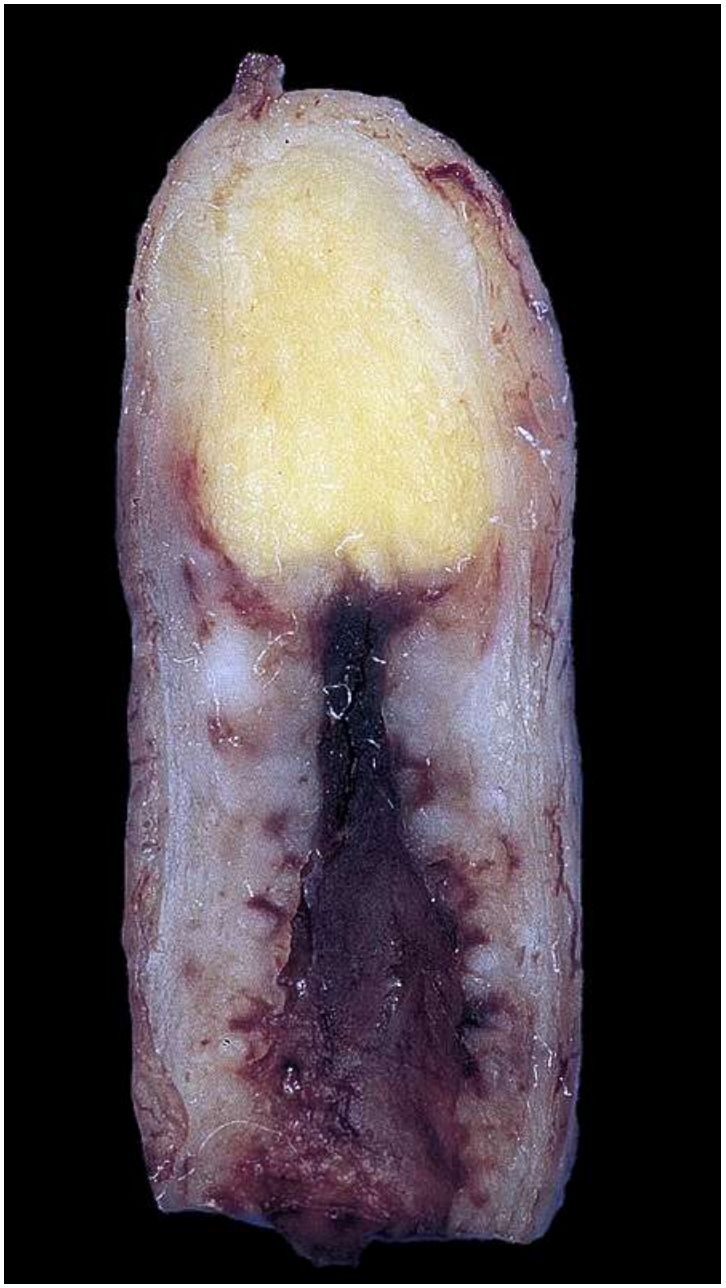
Majority are small tumors spanning **<2 cm**

Tumors metastasize first to **regional lymph nodes followed by liver.**

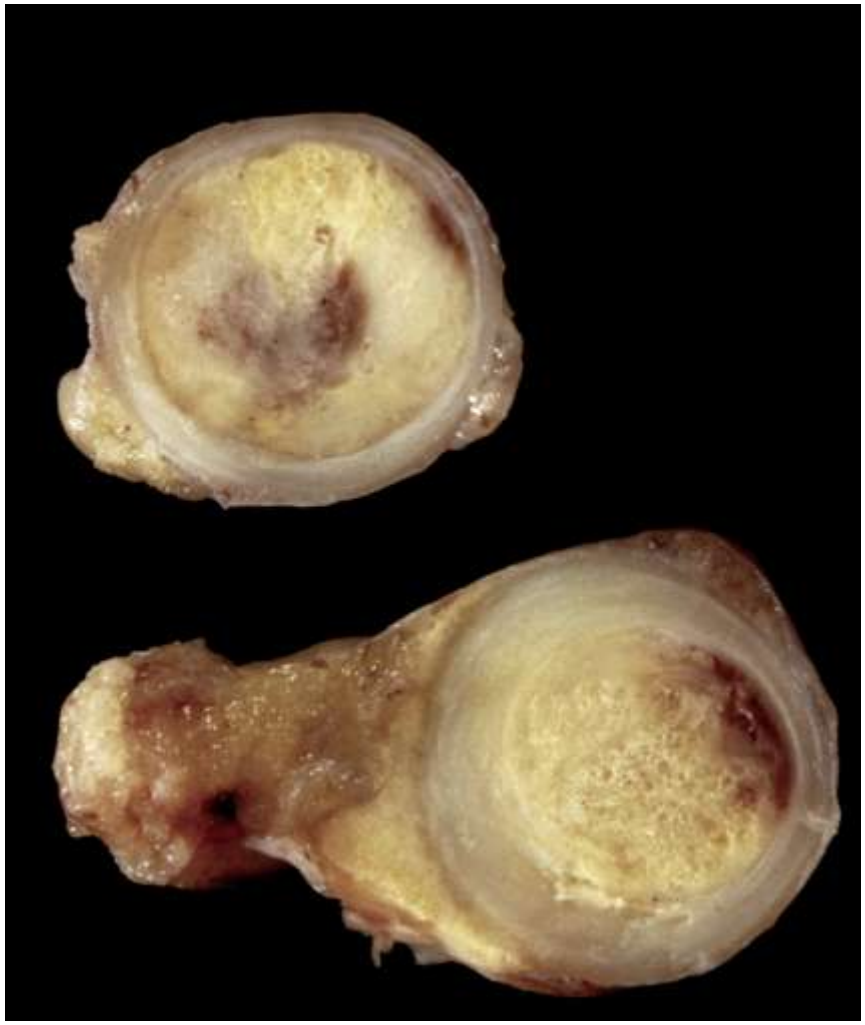
Small lesions up to 1 cm are generally treated with **appendectomy alone**

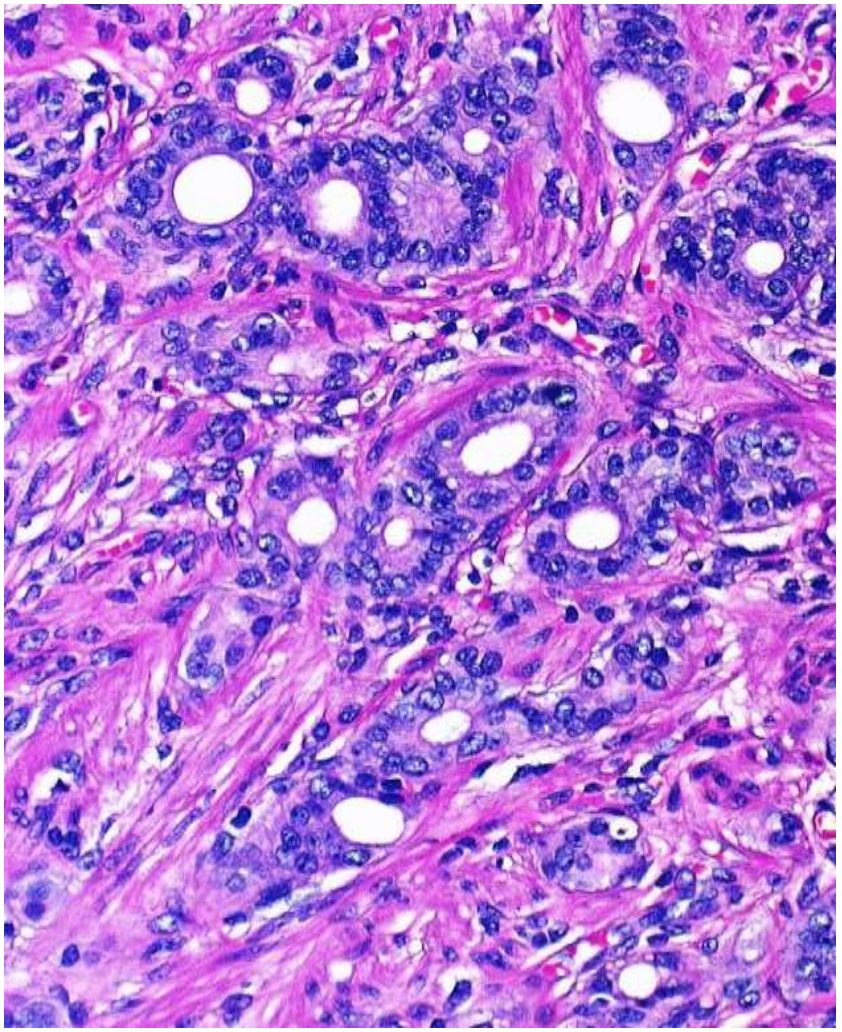
Right colectomy with lymph node dissection is considered when tumors are >2 cm

Tumor grading is assigned based on a combination of **mitotic activity and extent of Ki-67 staining.**

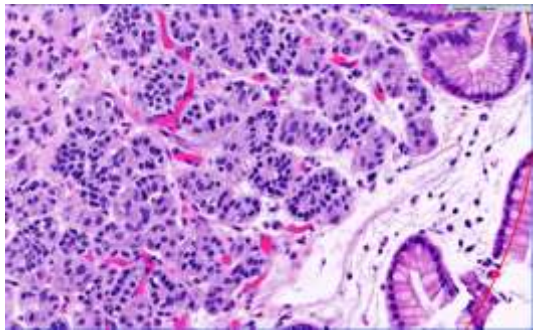


Neuroendocrine tumor

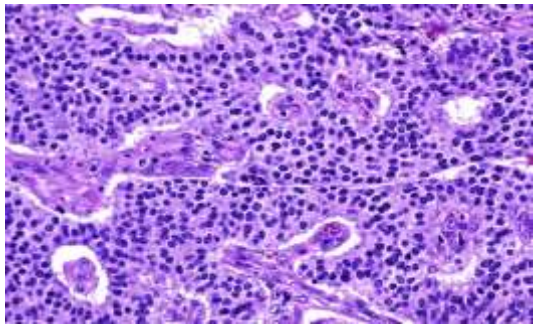




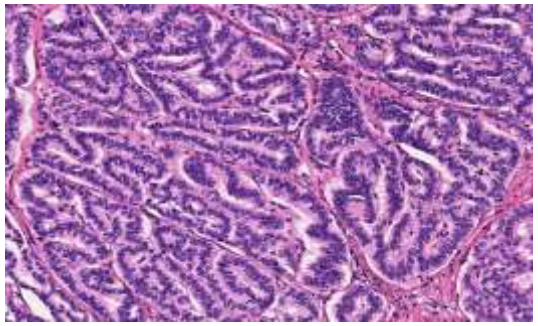
Enterochromaffin cell endocrine neoplasm (classic carcinoid tumors)
Similar to ileal NETs
Strongly positive for **chromogranin A, synaptophysin and serotonin**

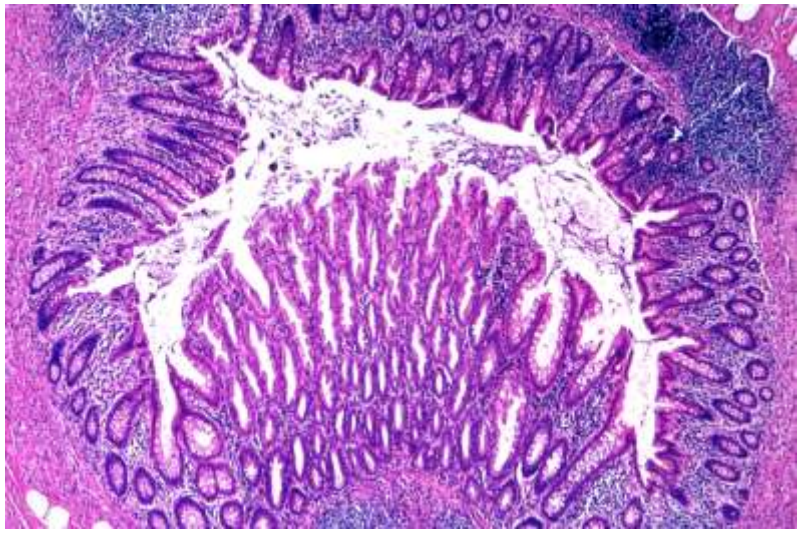


Enteroglucagon (L) cell endocrine neoplasm
Produce **enteroglucagon, glucagon-like peptides, pancreatic polypeptide and peptide YY.** Stain for chromogranin B, glucagon, and CEA, but are **negative for chromogranin A.**

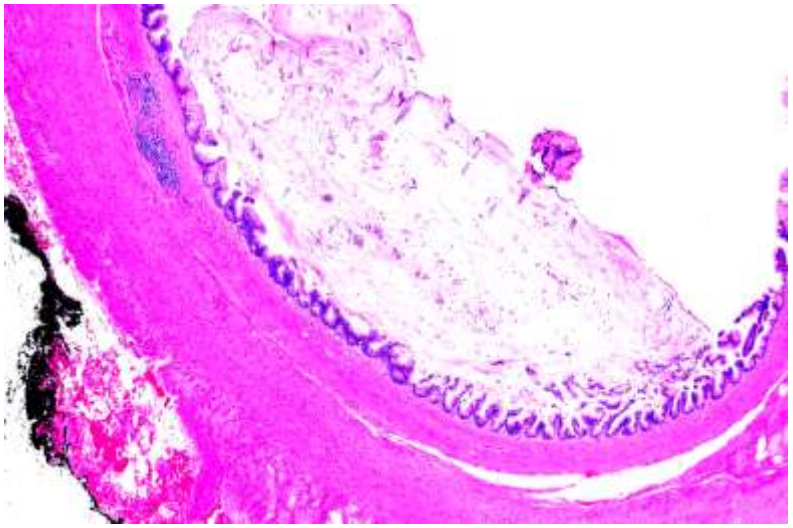


Tubular endocrine neoplasm
Positive for chromogranin B and glucagon
Negative for chromogranin A

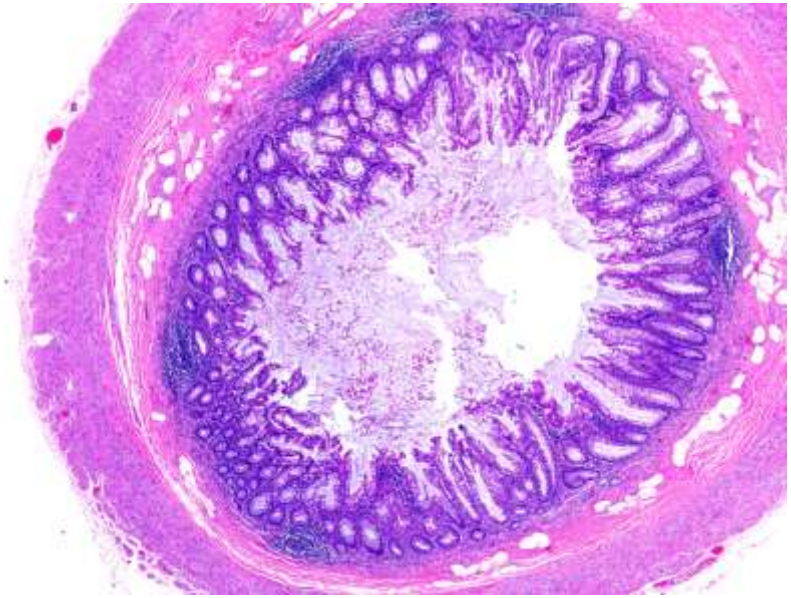




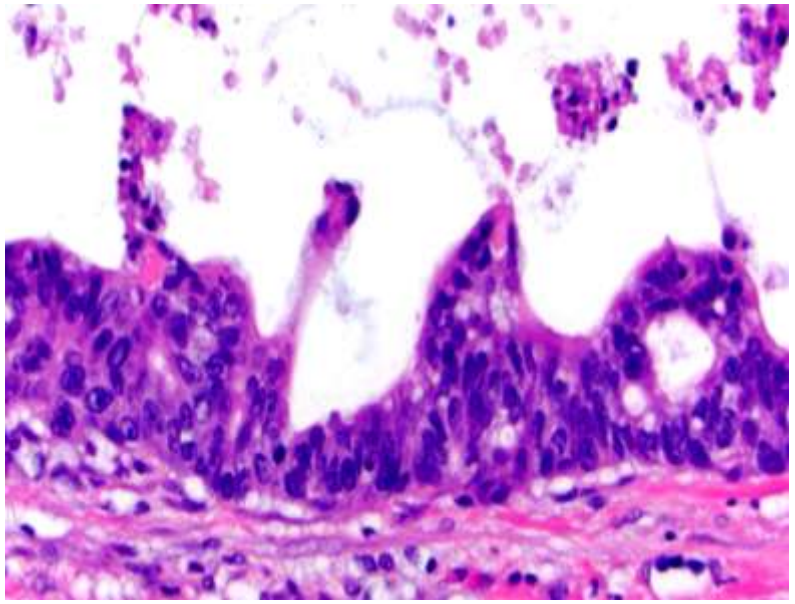
Serrated polyp



LAMIN – Low grade



Serrated polyp



LAMIN – High grade

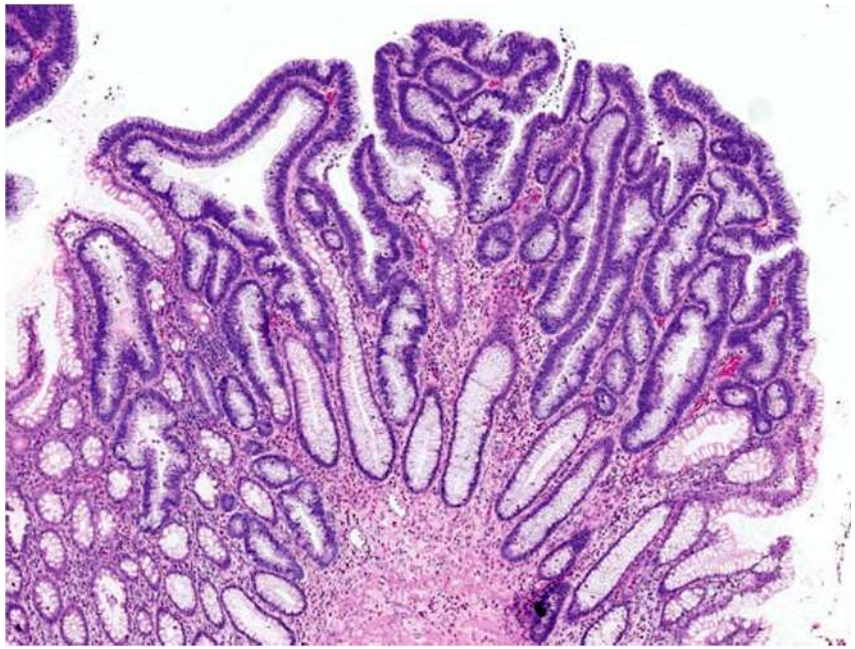
Conventional (colonic-type) appendiceal adenoma

Resemble conventional adenomas of the colon

Detected in appendicectomy specimens

Some represent extension of cecal adenomas

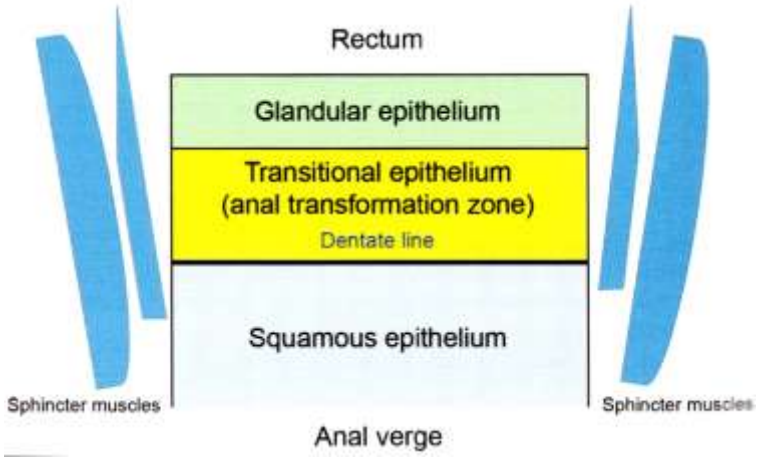
Do **not** involve the full circumference of the lumen

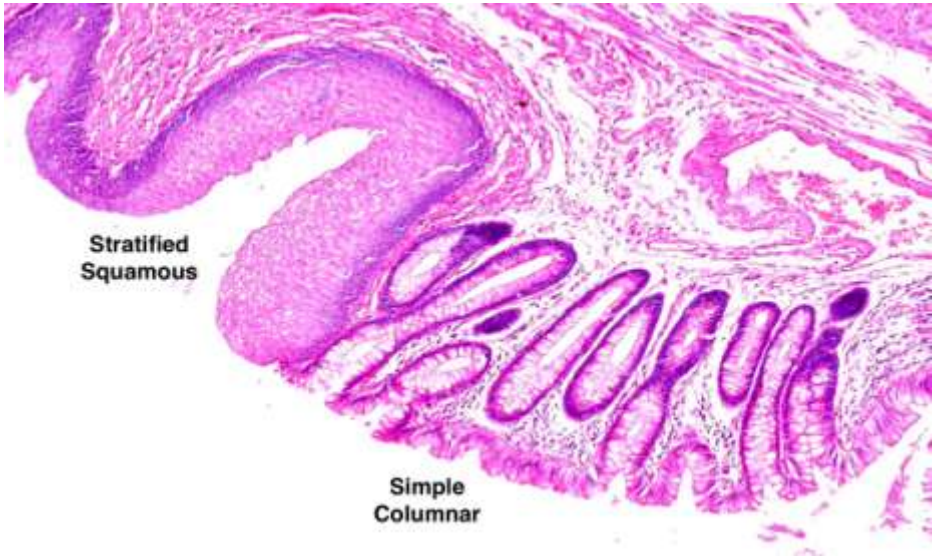


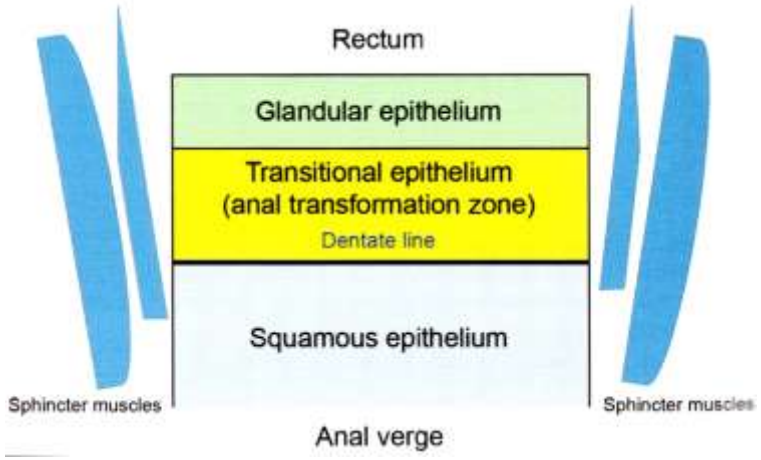
Anal Canal

Malignant epithelial tumours

8070/3	Squamous cell carcinoma NOS
8051/3	Verrucous squamous cell carcinoma
8140/3	Adenocarcinoma NOS
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)







Neoplasms of the anal canal

Complex array of neoplasms

Nomenclature is confusing

WHO recognizes: **squamous cell carcinoma (SCC), adenocarcinoma and neuroendocrine neoplasms**

Neoplasm	Site of Origin in Anal Canal		
	Colorectal Zone (Upper)	Anal Transitional Zone (Middle)	Squamous Zone (Lowest)
Adenocarcinoma of colorectal type	+		
Squamous cell carcinoma		+	+
Melanoma		+	+
Neuroendocrine tumor	+		
Small cell carcinoma[a]	+	+	
Mucinous adenocarcinoma[b]		+	

Anal adenocarcinoma

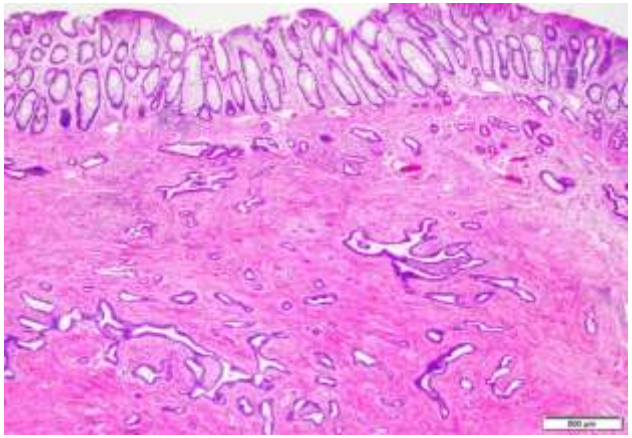
Arise in the **glandular epithelium** of the anal canal

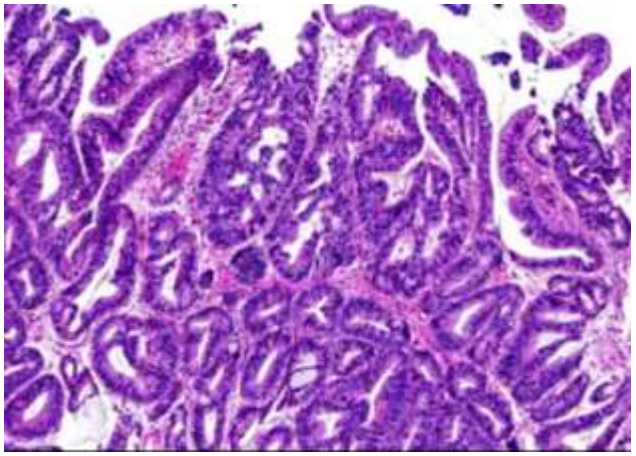
Two subtypes exist: **mucosal and extramucosal**

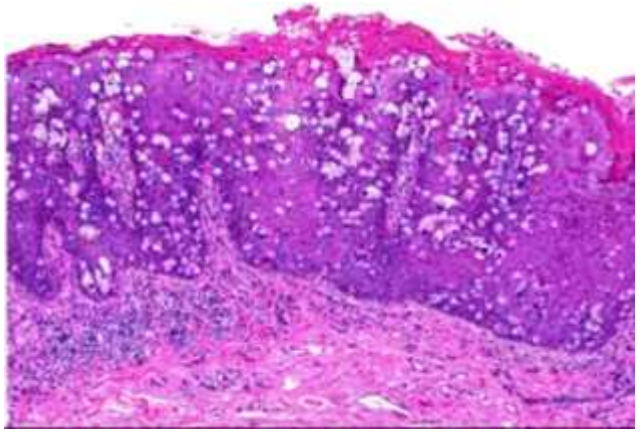
Mucosal ADC arises in the luminal mucosa and is of **intestinal type**

Extramucosal ADC may be associated with **anal gland, a pre-existing anal fistula or other non-fistulating glandular structures** of the anal canal (acquired or congenital malformations or embryological remnants)

May be of **anal gland type, mucinous type or intestinal type.**







Anal squamous cell carcinoma (SCC)

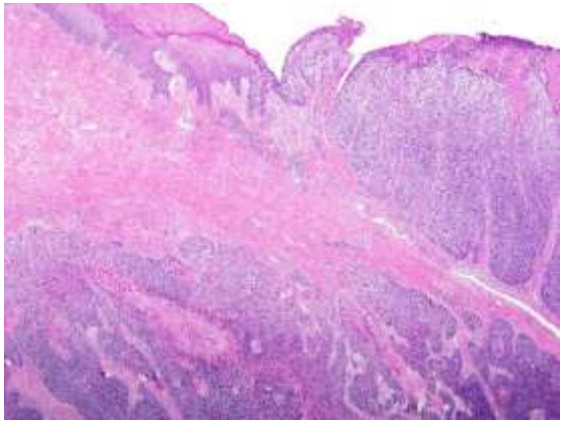
Originate from the anal mucosa and frequent **HPV associated**

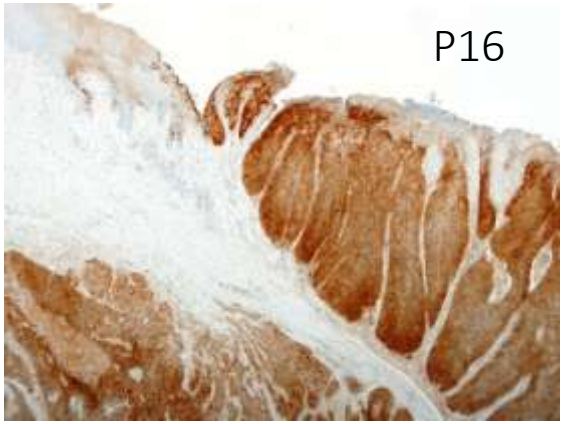
Can be **keratinizing, verrucous, urothelial-like, basaloid or mixed (squamous and mucinous)**

Histological features of the tumor are of **no clinical significance**

Squamous Lesion Description	Anal Intraepithelial Neoplasia (AIN)	Anal Squamous Intraepithelial Neoplasia (ASIN)	Lower Anogenital Squamous Terminology (LAST) Project
Condyloma acuminatum	Condyloma acuminatum	Condyloma acuminatum	LSIL (condyloma acuminatum)
Mild squamous dysplasia	AIN 1	ASIN-L	LSIL
Moderate squamous dysplasia	AIN 2	ASIN-H	HSIL
Severe squamous dysplasia	AIN 3	ASIN-H	HSIL
"Carcinoma in situ"	AIN 3	ASIN-H	HSIL

HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.





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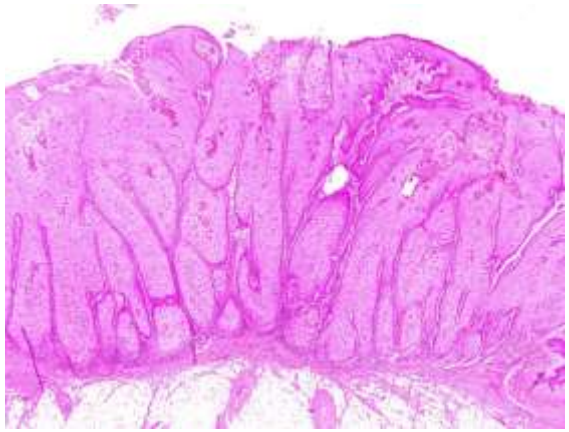
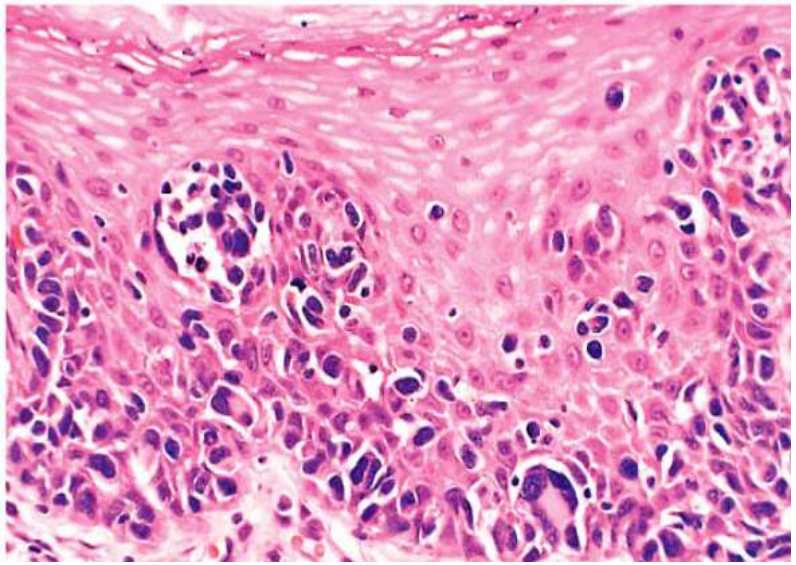
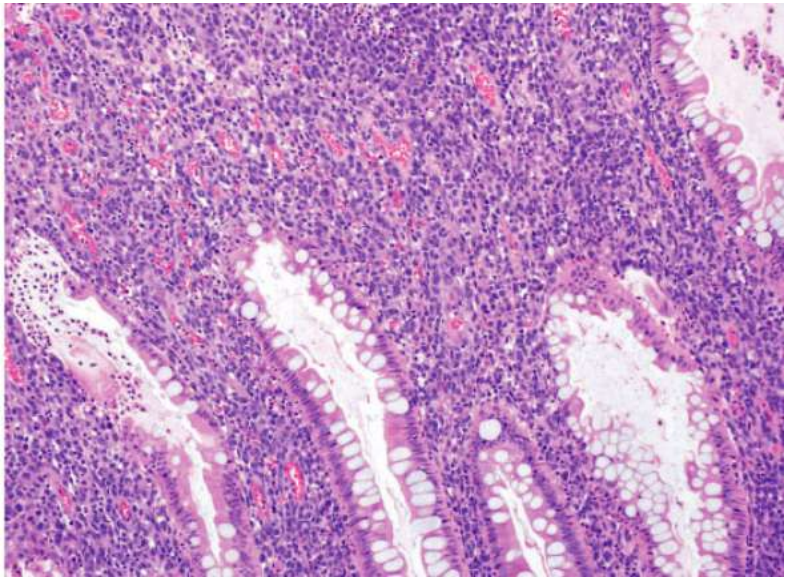






Anal melanomas (AMs)

Account for about 1% of all melanomas, usually present clinically with rectal bleeding, pain and a mass (same presentation as hemorrhoids, anal polyps or SCCs)

Detected late in their course and are advanced tumors at the time of diagnosis

Frequently polypoid, possibly pigmented, and located at or adjacent to the dentate line

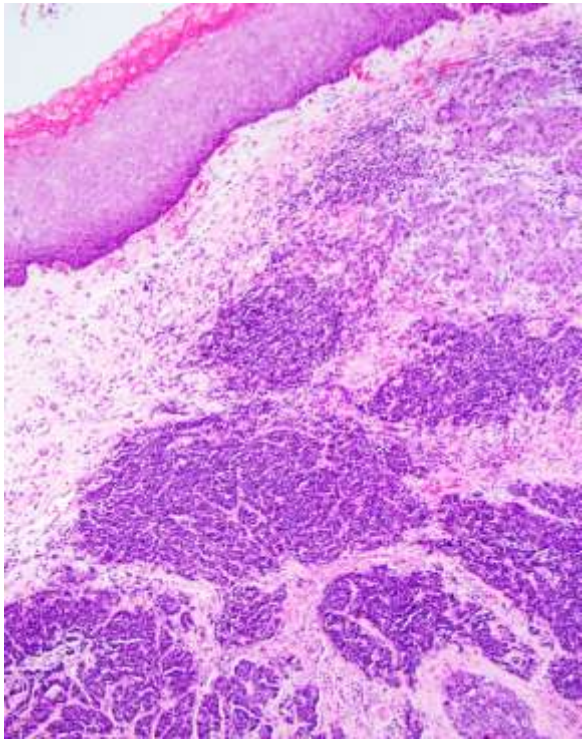
Same range of features and immunohistochemical reaction patterns as melanomas of the skin

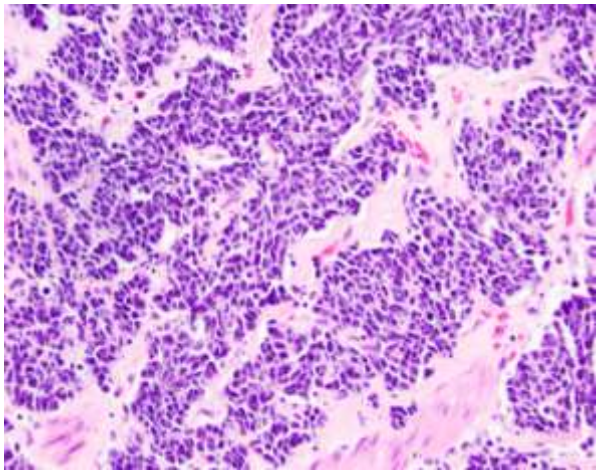
Neuroendocrine neoplasms (NENs) of the anal canal

Anal epithelial neoplasms with neuroendocrine differentiation.

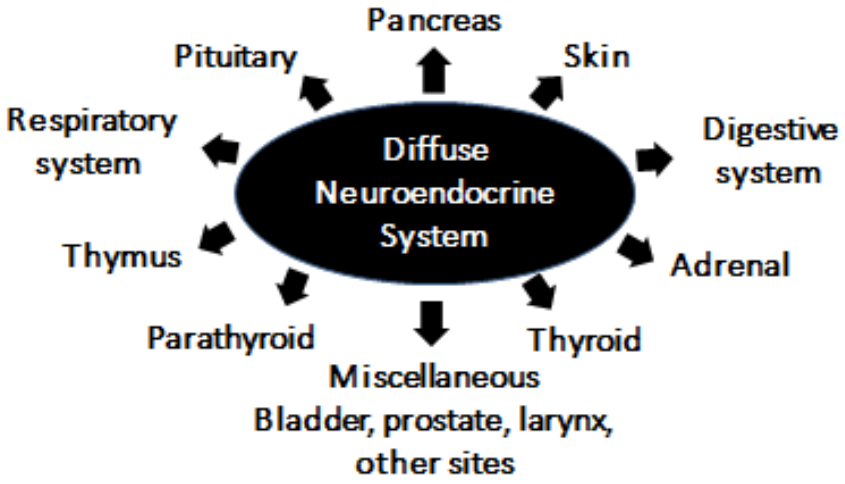
Malignant epithelial tumours

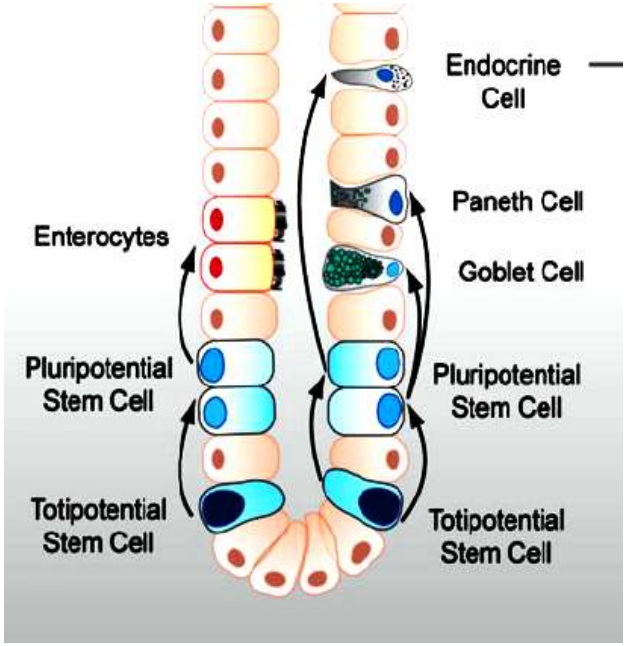
8070/3	Squamous cell carcinoma NOS
8051/3	Verrucous squamous cell carcinoma
8140/3	Adenocarcinoma NOS
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)





Neuroendocrine Neoplasms (NEN)





Diffuse Neuroendocrine System

Neuroendocrine cells are present in **all epithelial site**

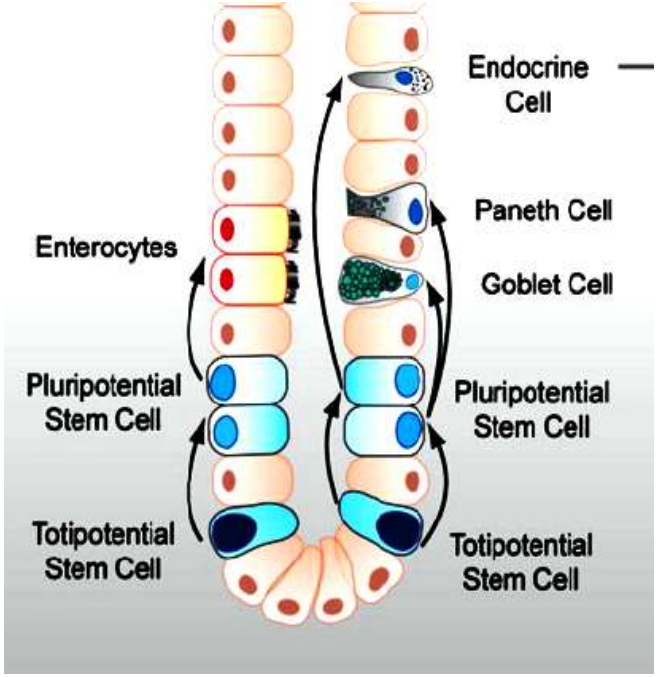
Neuroendocrine cells are the **largest group of hormone producing cells in the body**

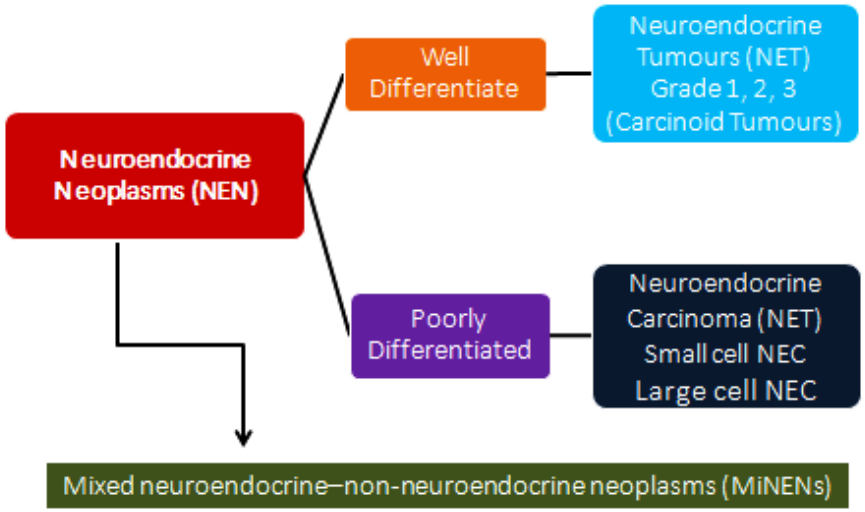
Neuroendocrine cells and their tumors can be identified by **morphology, NE markers or hormones they produce**

Commonly used NE markers are **Chromogranin, Synaptophysin, CD56, etc**

INSM1 (Insulinoma-associated protein 1) and **HE4** (Human epididymis protein 4) are among the latest neuroendocrine markers

Neuroendocrine cells give rise to **neuroendocrine neoplasms (NEN)** which as classified as **Neuroendocrine tumors (NET)** and **neuroendocrine carcinomas (NEC)**




Neuroendocrine Neoplasms (NEN)
Well Differentiate
Neuroendocrine Tumours (NET) Grade 1, 2, 3 (Carcinoid Tumours)
Poorly Differentiated
Neuroendocrine Carcinoma (NET) Small cell NEC Large cell NEC
Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs)

Diffuse Neuroendocrine System

Neuroendocrine (NE) cells

Originate locally from totipotential stem cells in all epithelial sites

↓

Neuroendocrine Neoplasms (NEN)

Neuroendocrine tumor (NET)

Well differentiated NEN

Grade 1, 2, 3

(Carcinoid tumor)

Neuroendocrine carcinoma (NEC)

Poorly differentiated NEN

Small cell NEC

Large cell NEC

Mixed NE–non-NE neoplasms (MiNENs)

Endocrine component constitutes

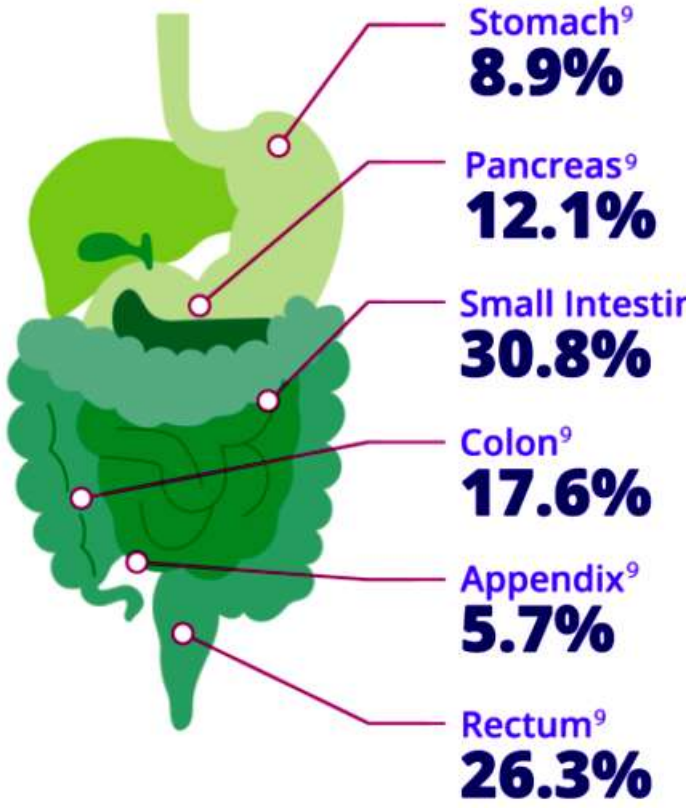
≥ 30% of the neoplasm

Neuroendocrine neoplasms (NENs) are epithelial tumors that occur in all epithelial sites with an annual incidence of up to 5 per 100000

- Digestive system 65%
- Respiratory system 25%
- Other primary sites 10%

GI Tract NEN

- Small intestine 50%
- Stomach 10%
- Rectum and colon 30%
- Appendix 10%



Lung
Atypical

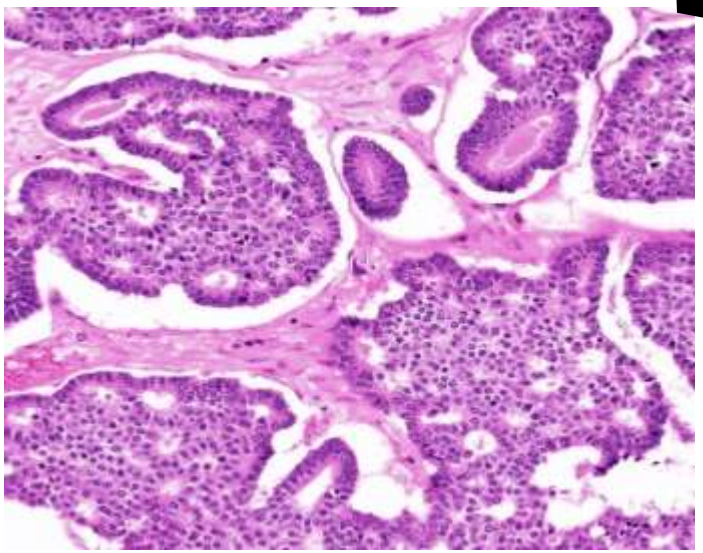
Appendix
Benign

Ileum
Malignant

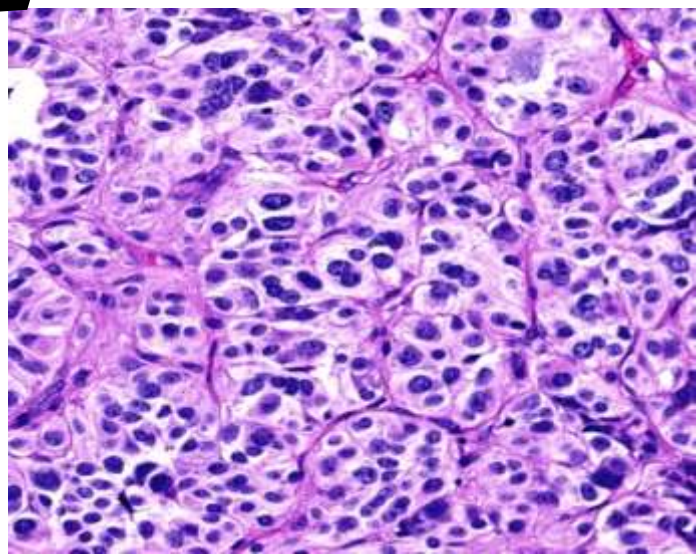
Carcinoid
tumor

Pancreas
Insulinoma

Stomach
Gastrinoma



“Carcinoid”



“Carcinoid”

Carcinoid tumor

- **Carcinoid** introduced in 1897 by the Russian Histologist, Nikolai Kulchitsky to describe a unique type of cell within the intestinal epithelium

- Carcinoid tumors have **diverse histology, hormone production, molecular profile and clinical behaviour**

- **Terminology** varies by site, type and hormone secretion inappropriate

- **Consensus meeting 2017** suggested a single classification for all **neuroendocrine tumors (NET)** in all sites

- **Neuroendocrine tumor to replace carcinoid tumor**

- **Terminology adopted by WHO classification of tumors in 2019**

Current classification of neuroendocrine neoplasms (NENs)

1. **Morphology** (neuroendocrine features)

2. **Positivity for at least one pan neuroendocrine marker** (Chromogranin A, Synaptophysin, CD56)

3. Tumor grade

   Well differentiated neuroendocrine tumor (NET)

   Poorly differentiated neuroendocrine carcinoma (NEC)

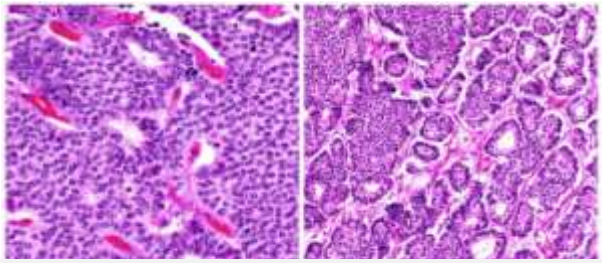
4. Mitotic rate

   Mitotic rate/2 mm sq

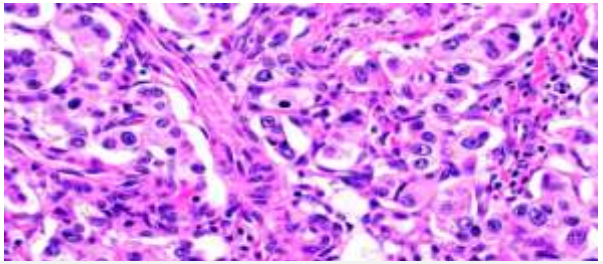
   <2, 2-20, >20

5. Proliferation index (PI)

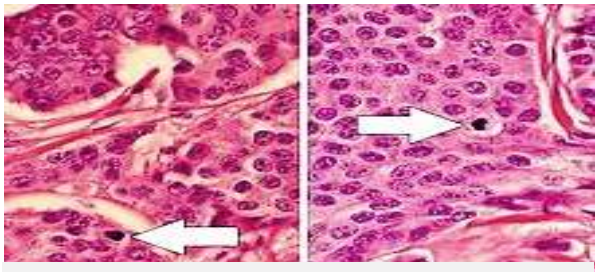
   Ki-67 by IHC <3%, 3-20%, >20%)



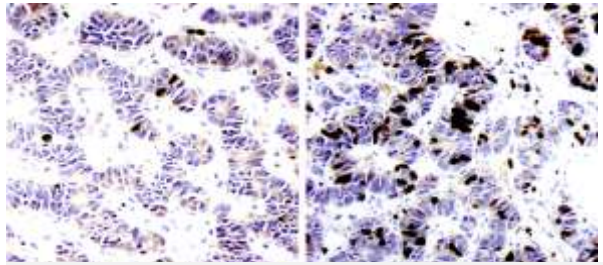
Well differentiated NET



Poorly differentiated NEC



Mitotic figures



PI by Ki67

Classification of neuroendocrine neoplasms (NEN)

Well Differentiated Neuroendocrine Neoplasms (NETs)	Poorly Differentiated Neuroendocrine Neoplasms (NECs)
Grade 1 Ki67 <3%, Mitotic rate <2/2mm sq	All have Ki67 >20%, Mitotic rate >20/2mm sq
Grade 2 Ki67 3-20%, Mitotic rate 2-20/2mm sq	Small cell Neuroendocrine carcinoma
Grade 3 Ki67 >20%, Mitotic rate >20/2mm sq	Large cell Neuroendocrine carcinoma

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN)
Neuroendocrine and non-neuroendocrine components
Each component is distinct (NEC and ADC) and constitutes ≥30% of the neoplasm.
Ki67: >20; Mitotic rate: >20/2mm sq

NENs are defined by morphology and neuroendocrine markers positivity
NENs are graded by mitotic rate and proliferative index
Malignant NEN s are defined by Ki67 >20% or Mitotic index of >20/2mm sq
Type of malignancy is determined by morphology (small cell or large cell)

Neuroendocrine neoplasms of the digestive system			
Location	Foregut	Midgut	Hindgut
Behaviour	Variable site and type dependant	Aggressive when necrosis and mitoses present	Variable benign when low mitoses and no necrosis
Number	Single/multiple	Multiple	Single
Hormones	Gastrin Somatostatin	Serotonin	Polypeptides Enteroglucagon VIP

The seemingly same tumor has widely differing symptomatology, morphology and clinical outcome in different locations

Foregut (oral cavity to the middle of the duodenum)
Midgut (middle of the duodenum to the first two-thirds of the transverse colon)
Hindgut (distal third of the transverse colon to the upper part of the anus)

Gastric Neuroendocrine Neoplasms				
Type	Frequency	Background	Site & No.	Behaviour
I	75%	Atrophic gastritis Achlorhydria	Body Multiple	Low PI (<3%), indolent, No mets, 100% survival
II	5%	Gastrinoma in the duodenum or pancreas (ZES, MEN 1)	Body Multiple	Intermediate PI up to 20%, mets in >10%, 70% 5 year survival
III	15%	No clinical association	Any part Solitary	High PI >20%, mets in >50%, <50% survival
Provisional type IV G-NETs are caused by defective parietal cell H+/K+ adenosine triphosphatase (ATPase) pump, which leads to inadequate acid secretion and compensatory antral G-cell hyperplasia and hypergastrinemia				
Provisional type V G-NETs has recently been described in patients who have been on long-term PPI therapy but do not have chronic autoimmune atrophic gastritis, gastrinoma or MEN-1 syndrome				

>90% of gastric NENs are benign or neuroendocrine tumors (NETs)
~10% of gastric NENs are either NECs or MiNENs

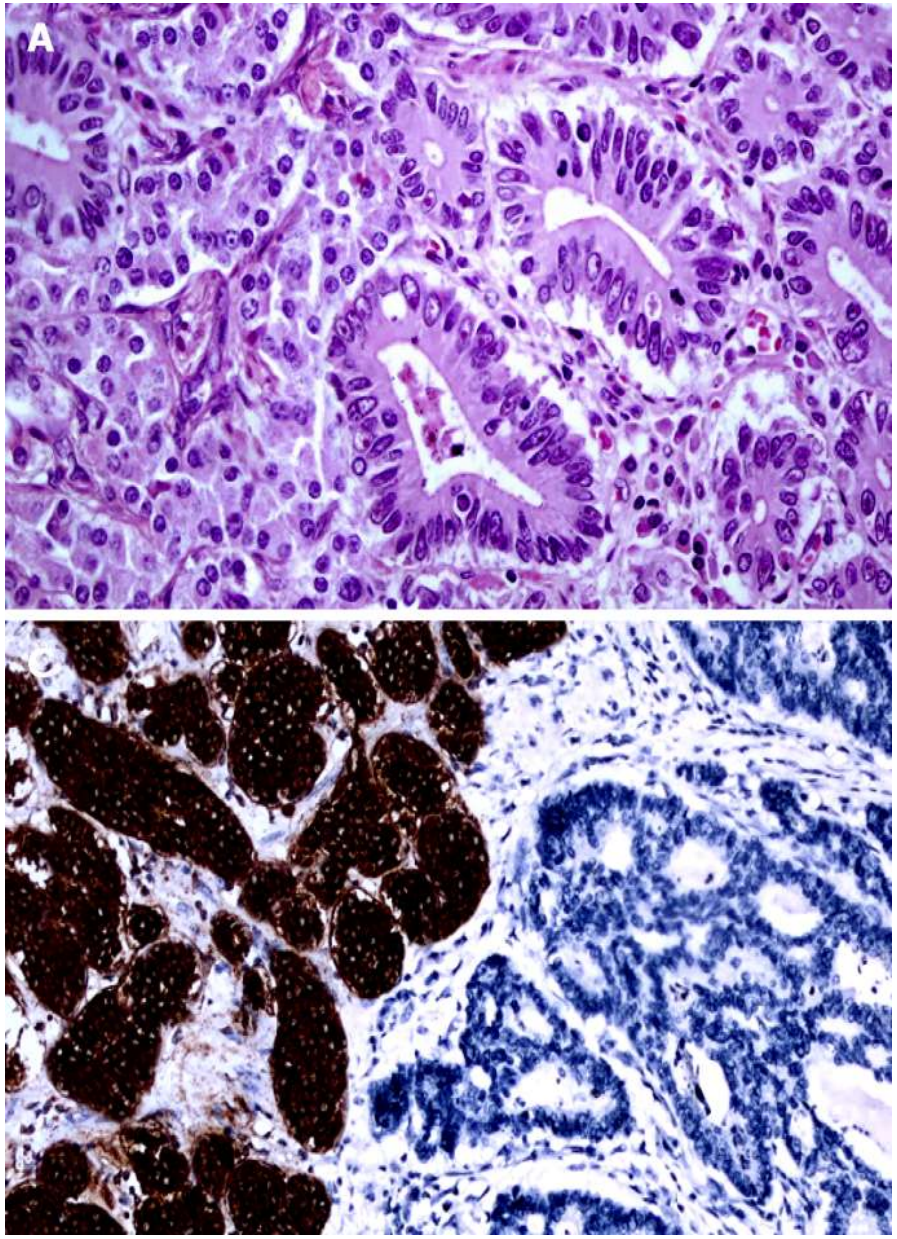
Characteristics of the subtypes of neuroendocrine neoplasms of the stomach

	Type 1	Type 2	Type 3	Type 4
Proportion	70%-80%	5%	10%-25%	Rarely
Pathogenesis	Increased gastrin levels due to atrophic gastritis. ECL origin	Increased gastrin levels due to gastrinoma. ECL origin	Not known. Mostly ECL origin	Not known. Non-ECL origin
Location and characteristics	Gastric body and fundus. Often small and multiple	Gastric body and fundus. Often small and multiple	Anywhere. Large and solitary	Anywhere. Large (often larger than type 3)
Gastrin level	Increased	Increased	Normal	Increased or normal
Prognosis	Excellent	Good	Bad	Bad
Treatment	Surveillance without resection, Endoscopic resection, surgery	Endoscopic or surgical resection, resection of gastrinoma	Gastrectomy and regional lymphadenectomy, systemic chemotherapy	Gastrectomy and regional lymphadenectomy, systemic chemotherapy

Small Bowel Neuroendocrine Neoplasms		
Duodenal	**Ampullary**	**Jejuno-ileal**
Mostly **non-functioning** Some produce **Gastrin**	Mostly **Somatostatin** producing tumors	**Serotonin** producing tumors
Small sessile lesions in the mucosa of D1	Arise in the **ampullary and periampullary region**	Most occur in the **ileum**
Non-functioning tumors are isolated tumors **Gastrin producing tumors** may cause **ZES**	**Biliary obstruction** **Somatostatin syndrome** (hyperglycemia and steatorrhea)	**Can produce Carcinoid Syndrome** **Poor outcome** **LN &** liver mets at presentation
One-third may occur in the setting of **MEN 1**	May be associated with **NF type 1, vHL disease and pheochromocytoma**	**Not** associated with heritable cancer syndromes

Large Bowel Neuroendocrine Neoplasms	
Colon	**Rectum**
Least common site for NENs	**Relatively common**; Most (>90%) are <2 cm
Most (3/4) occur in the **proximal colon** **C**linical features similar to those of other **midgut neuroendocrine neoplasms**	Usually identified during **colonoscopy** (smooth, firm, circumscribed yellow nodules) Indolent tumors are small (<2cm) Aggressive tumors are larger (2cm)
Presents with abdominal **pain and masses** in the right lower quadrant	Incidental finding or presents with **rectal bleeding and pain** **Not** associated with any heritable disorders
Produce **serotonin** and can cause **carcinoid syndrome**	**Well-differentiated tumors** are mostly **enteroglucagon** producing
Regional **lymph node disease is seen in 50%** at diagnosis and 40% have **distant metastases**	Invasion of muscularis propria, vessels or nerves with increased risk of **recurrence or metastasis** may be seen in tumors **>2cm**

Mixed endocrine-non-neuroendocrine neoplasms (MiNEN)



Mixed neuroendocrine carcinoma and other carcinoma types, usually adenocarcinoma

One component has be at least 30% of the tumor

Pathology report

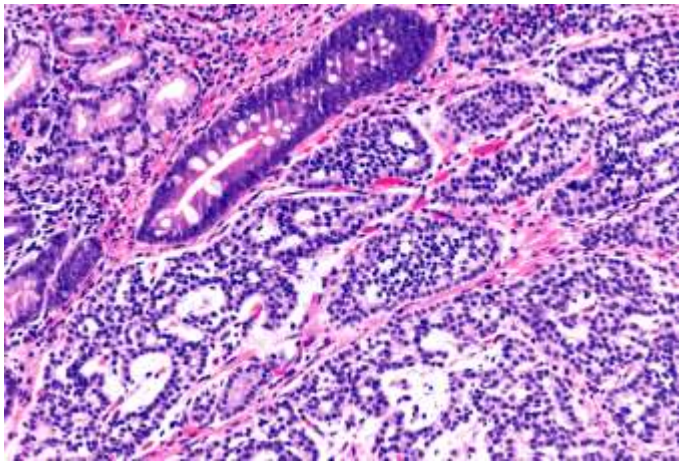
1. Diagnose of NEN on morphology

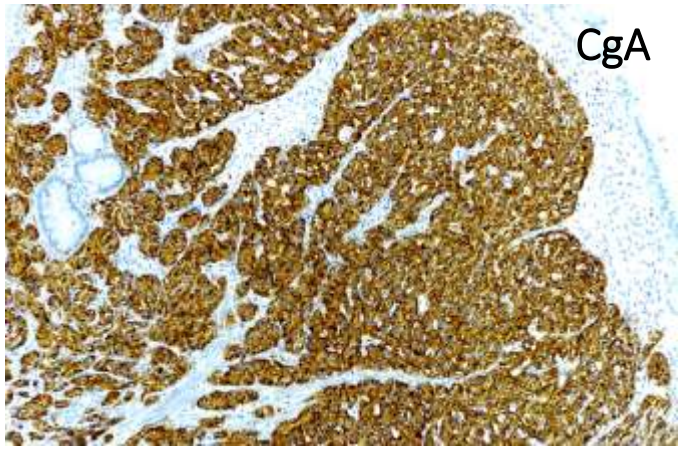
2. Confirm by positivity for a neuroendocrine marker (Chromogranin A, Synaptophysin, CD56, etc)

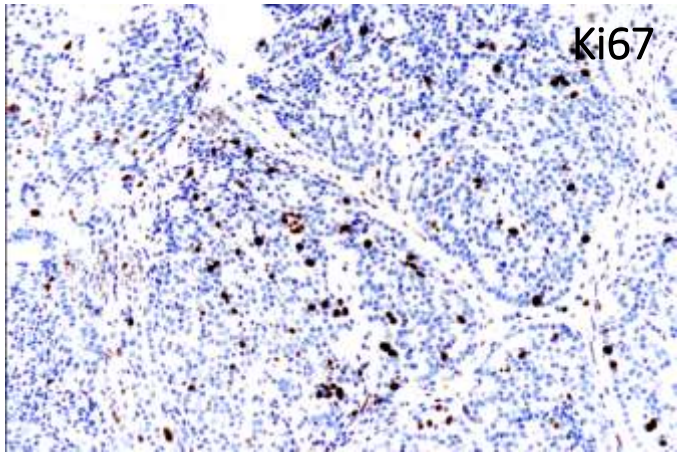
3. Categorize by degree of differentiation
   Well differentiated NE tumor (NET)
   Poorly differentiated NE Carcinoma (NEC)

4. Count mitotic rate (per 2 mm sq)

5. Determine proliferation index (Ki67% by IHC)







Conclusions

NETs and NECs tend to show **similar IHC expressions**

Intensity of IHC staining is less with high-grade (NEC) tumors

CD56 and CD57 tend to stain more intensely in high-grade than in low grade NETs

High-grade neuroendocrine tumors can also stain with **calcitonin**

NETs can be grouped by

- **Secreted hormone** (somatostatin, gastrin)
- **General IHC marker** Immunoreactivity (chromogranin and synaptophysin)
- **Various keratins (CK8, CK18, and CK35betaH11)**

NENs are generally **CK7 and CK20 negative**

Cytoplasmic CD10 staining is more common in **malignant** than in benign NENs

Gastrointestinal Stromal tumor (GIST)

Mesenchymal tumors of the digestive system

Benign

- Ganglioneuroma/ganglioneuromatosis
- Glomus tumour (all forms)[a]
- Granular cell tumour
- Haemangioma
- Inflammatory fibroid polyp
- Leiomyoma
- Lipoma
- Lymphangioma/lymphangiomatosis
- Mesenchymal hamartoma of the liver
- PEComa[a]
- Perineurioma
- Plexiform fibromyxoma
- Schwannoma

Intermediate (locally aggressive)

- Desmoid fibromatosis

Intermediate (rarely metastasizing; < 2%)

- Inflammatory myofibroblastic tumour
- Kaposi sarcoma
- Solitary fibrous tumour

Malignant

- Angiosarcoma
- Embryonal sarcoma of the liver
- Gastrointestinal clear cell sarcoma
- Gastrointestinal stromal tumor
- Leiomyosarcoma
- Rhabdomyosarcoma (all forms)
- Synovial sarcoma

Gastrointestinal Stromal Tumor (GIST)

Most common mesenchymal tumor of the GIT

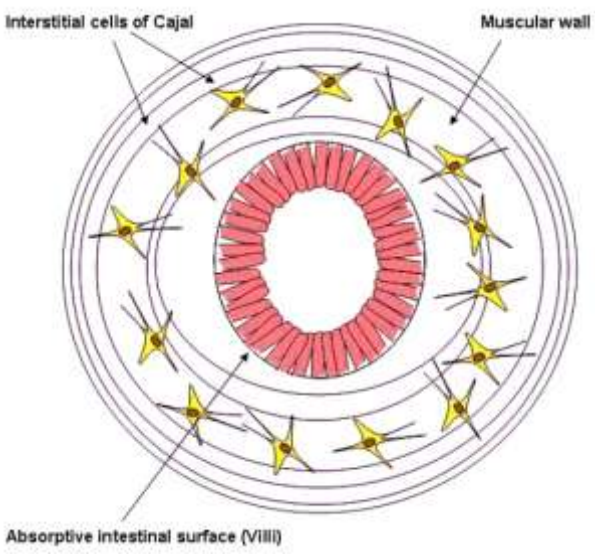
GIST is tumor of the Interstitial Cells of Cajal (ICC)

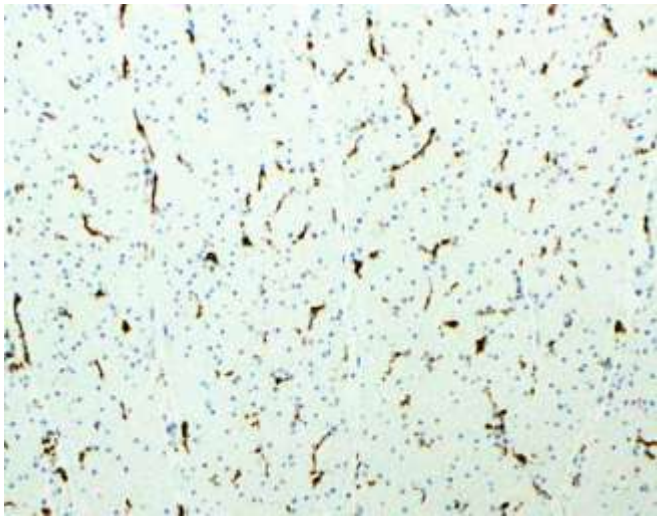
ICC is regarded as GI pacemaker cells

ICC transfers motor neural signals from the enteric nervous system to muscle

ICC responds to muscle stretch by generating and coordinating slow wave activity

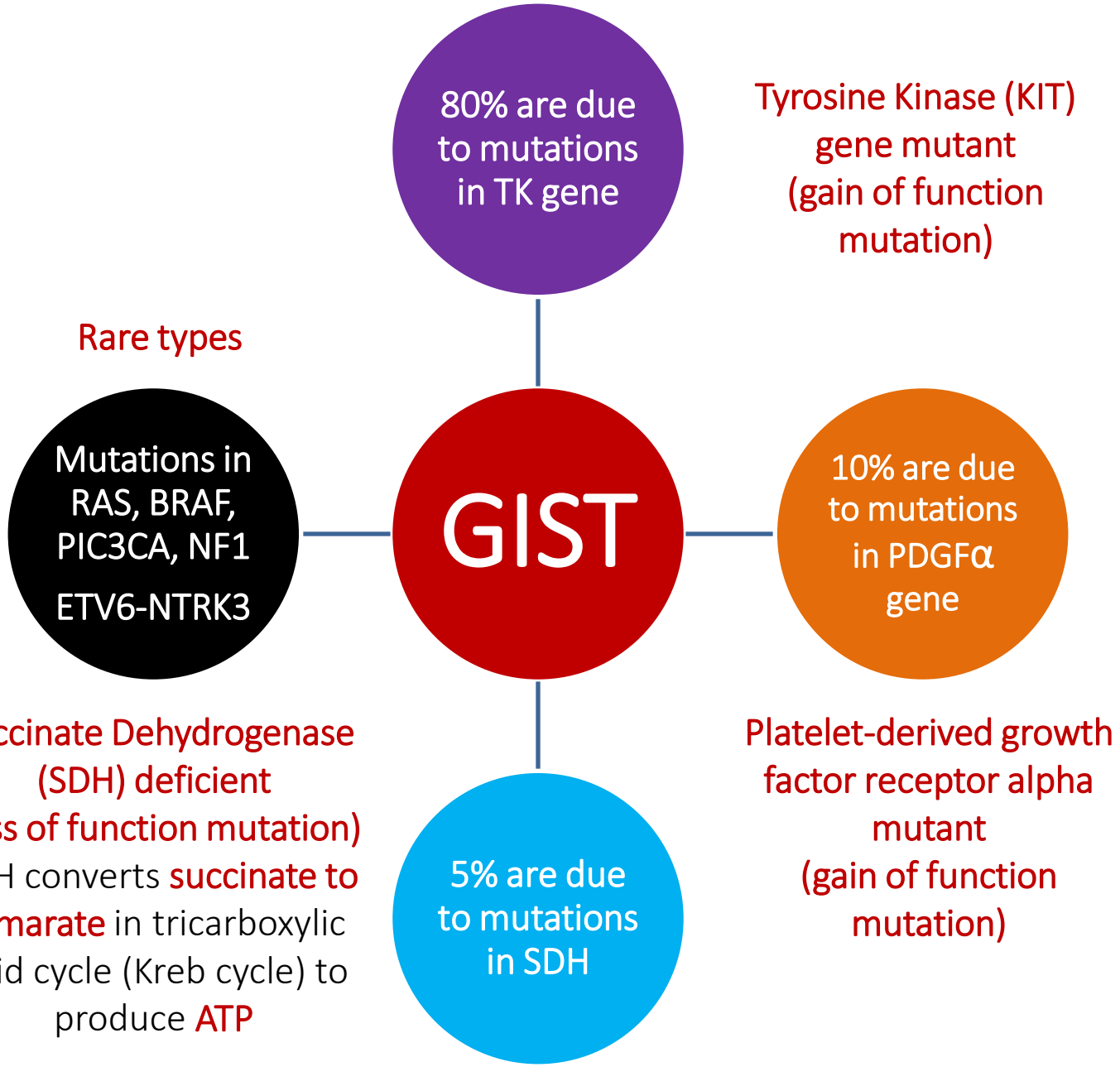
ICC can be demonstrated by CD34, CD117 (c-KIT), DOG 1, PDGFα, etc

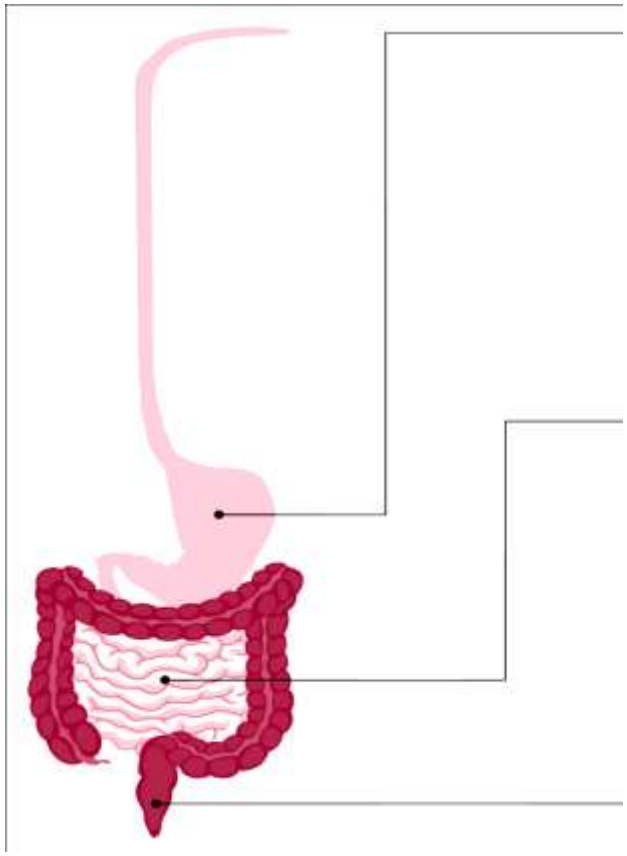




CD 117 (c-KIT)

Histologically GIST can have spindle cell or epithelioid morphology


80% are due to mutations in TK gene
Tyrosine Kinase (KIT) gene mutant (gain of function mutation)
Rare types
Mutations in RAS, BRAF, PIC3CA, NF1
ETV6-NTRK3
GIST
10% are due to mutations in PDGFα gene
Succinate Dehydrogenase (SDH) deficient (loss of function mutation)
SDH converts succinate to fumarate in tricarboxylic acid cycle (Kreb cycle) to produce ATP
5% are due to mutations in SDH
Platelet-derived growth factor receptor alpha mutant (gain of function mutation)



Stomach (commonest site)

55% of GI GISTs

65% show KIT mutations

20% show PDGFRα mutations

15% other mutations (SDH)

Small bowel

35% of GI GISTs

75% show KIT mutations

10% show PDGFRα mutations

15% other mutations (SDH)

Colorectum

6% of GI GISTs

90% show KIT mutations

10% show other mutations

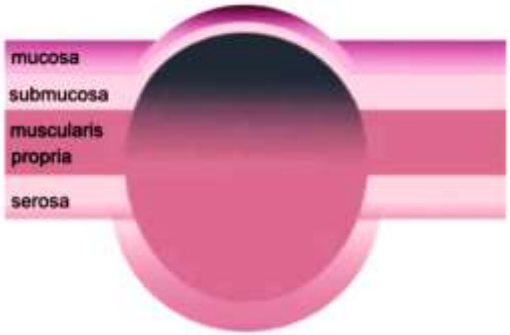
Global figures from 29 studies from 19 countries of 1**3,550 patients** showed the following distribution: **gastric (55.6%), small bowel (31.8%), colorectal (6.0%), other location (5.5%) and oesophagus (0.7%)**

GISTs are **mural** tumors with an epicenter in the **muscularis propria**

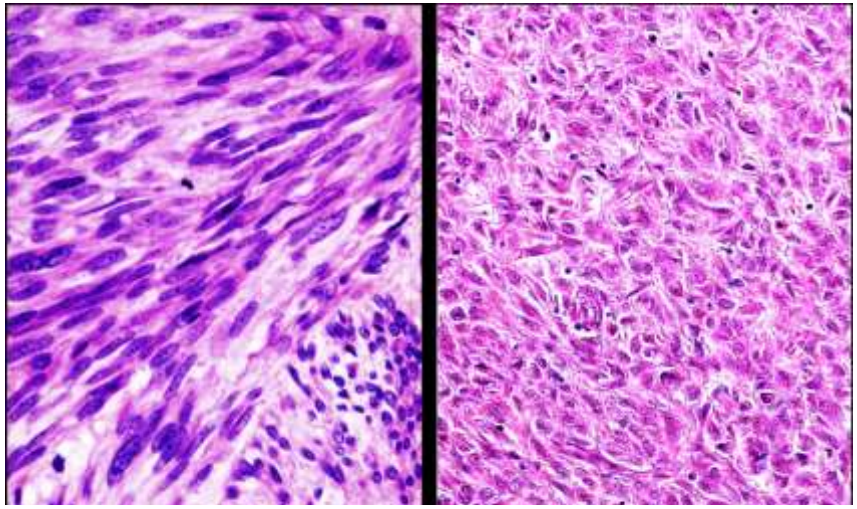
Circumscribed masses often with u**lceration, hemorrhage and cystic degeneration**

Most are **spindled cell type;** some have **epithelioid appearance**

Epithelioid type is seen especially in **SDH-deficient tumors**

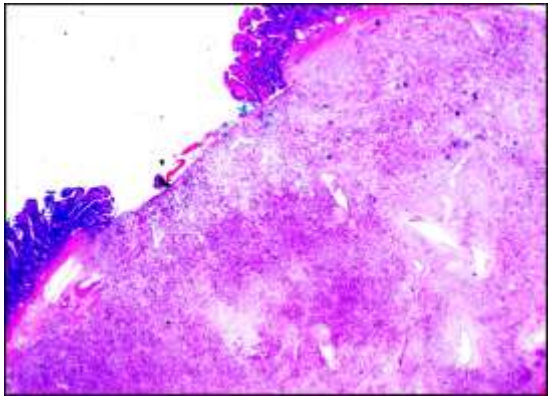


Ulcerated GIST



Spindle cell GIS

Epithelioid GIST



Ulcerated GIST

GIST spreading to the **peritoneum and liver**

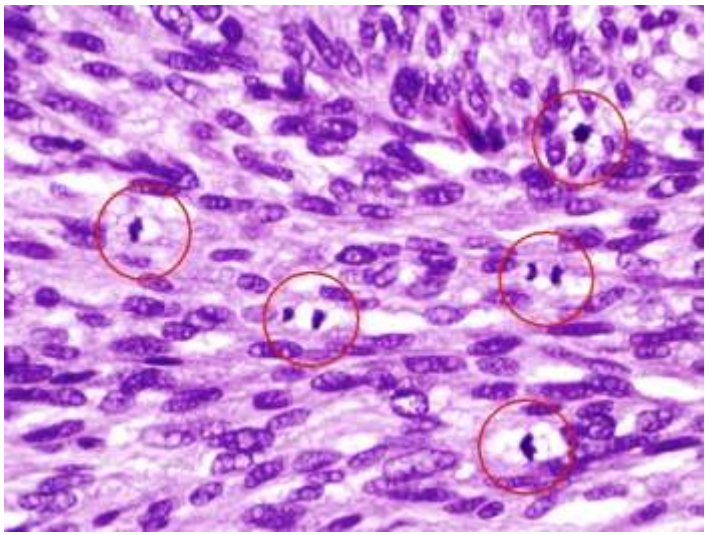
SDH-deficient tumors may metastasize to regional **lymph nodes**

Treatment consists of surgical resection without regional lymph node dissection

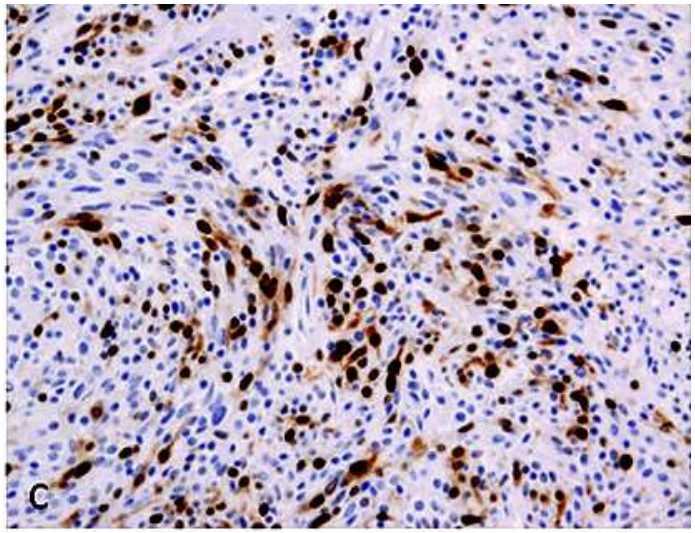
Patients with advanced (recurrent or metastatic) GIST are treated with **KIT inhibitors**

Most GISTs are **sporadic** but up to 10% occur in heritable syndromes (Carney syndrome , NF1)

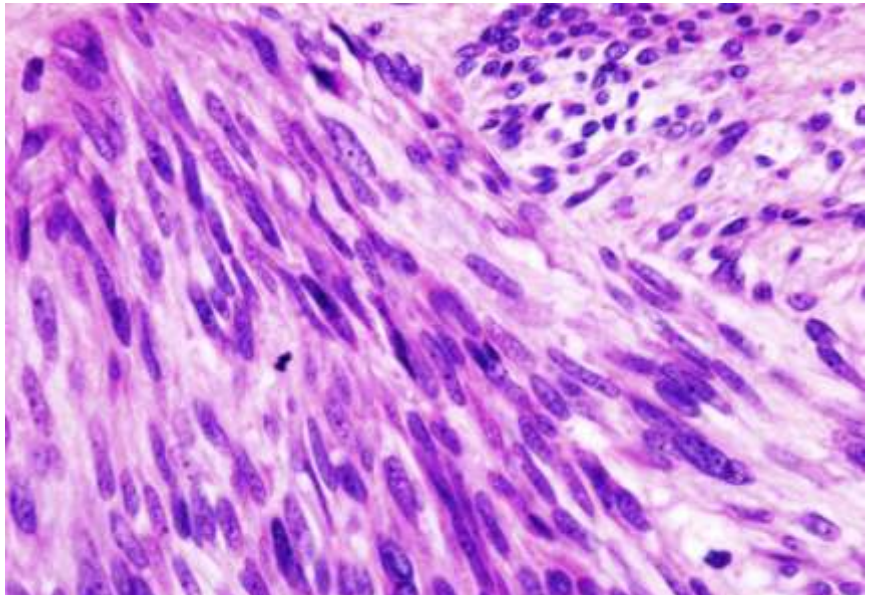
Risk stratification In GIST			
Size (cm)	Mitotic rate per 5mm sq (50 HPFs) and Ki67 index	Rate of progression by location Stomach	Small bowel
<5	<5	2%	4%
5-10	5-10	10%	50%
>10	>10	86%	90%



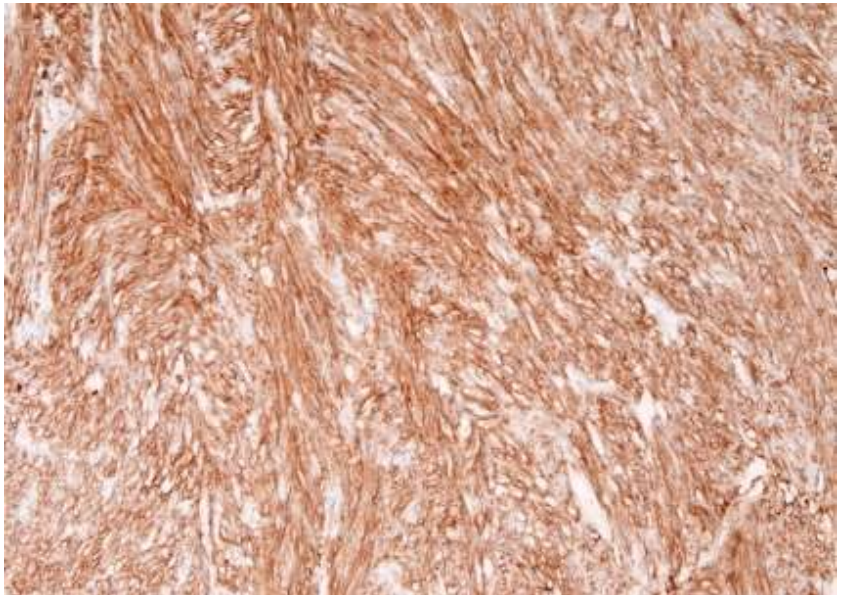
Mitotic rate and



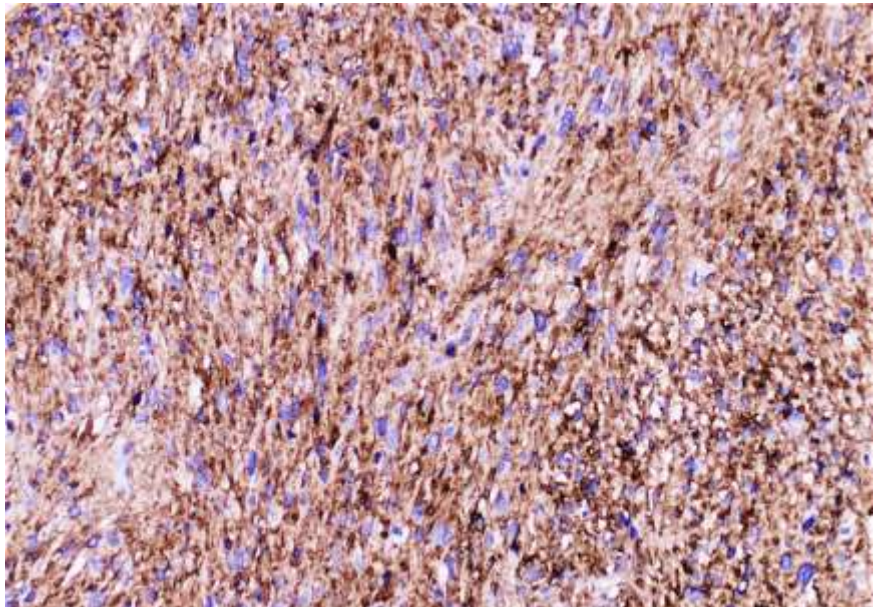
Ki67 index



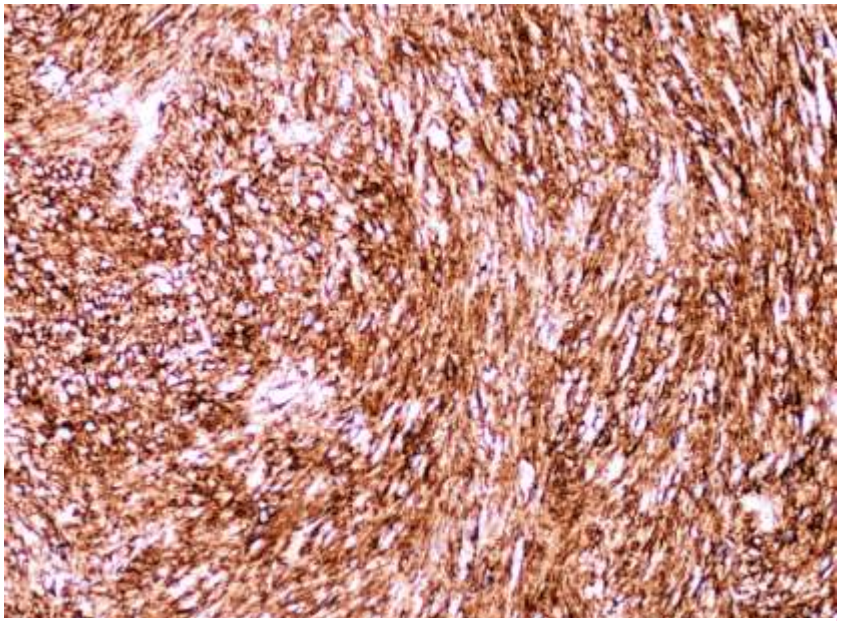
H&E



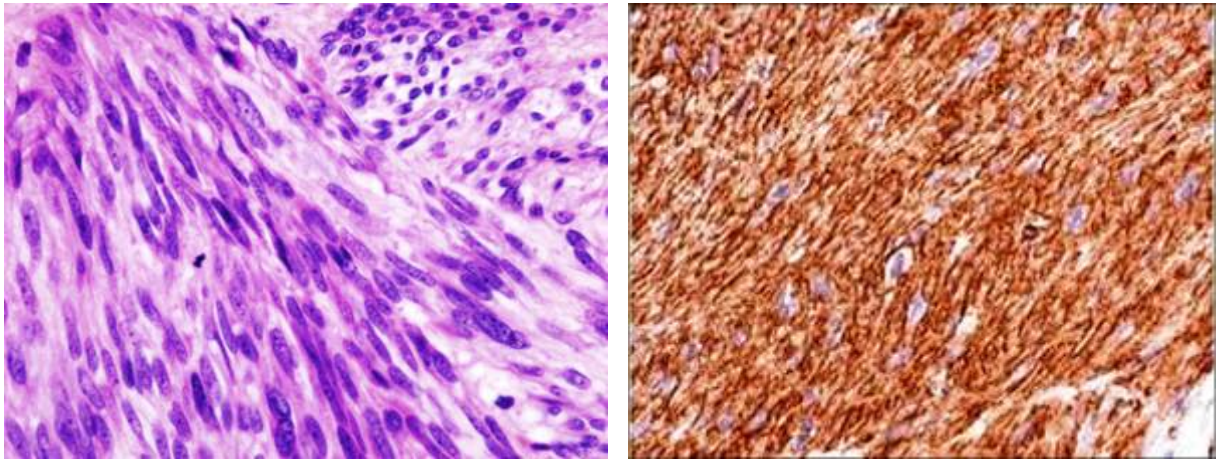
CD34



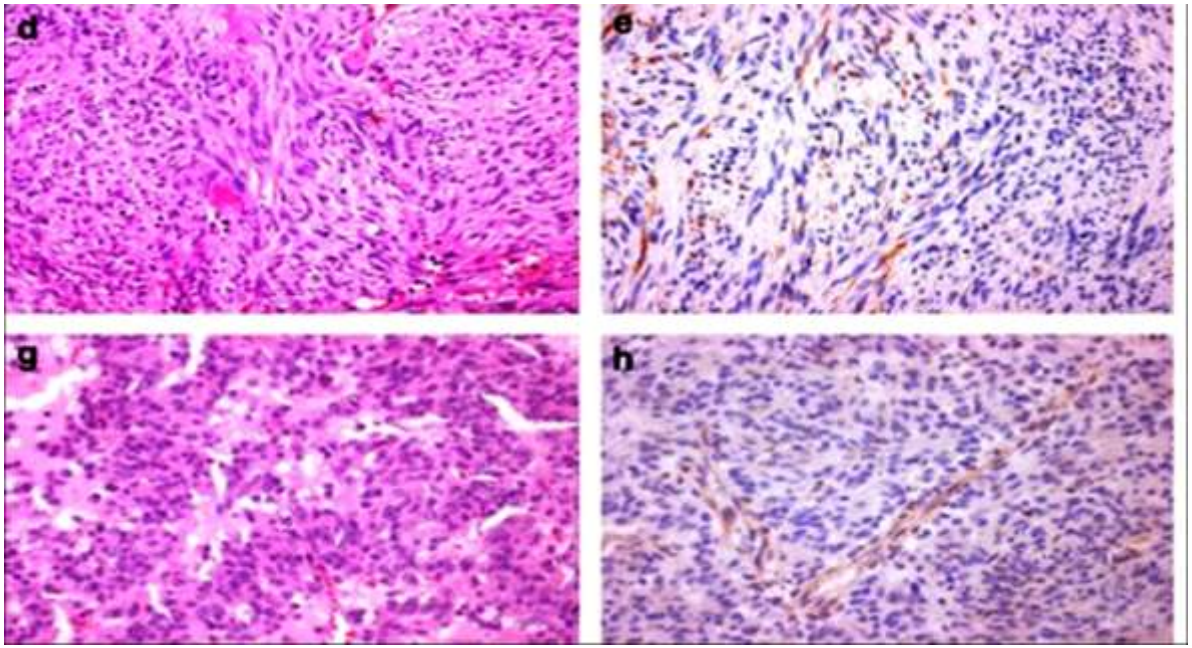
CD117 (c-KIT)



DOG1



PDGFα is positive staining (brown) in >10% of GISTs



SDH deficient GIST (negative staining in <5%) of GISTs

Diagnosis of GIST

Morphology

Spindle cell GIST or Epithelioid GIST

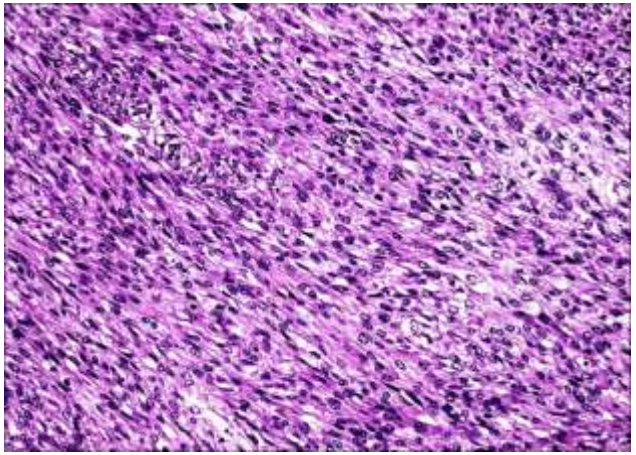
IHC

Positive: GIST markers (CD117, DOG1, CD34, PDGFα, SDH, etc)

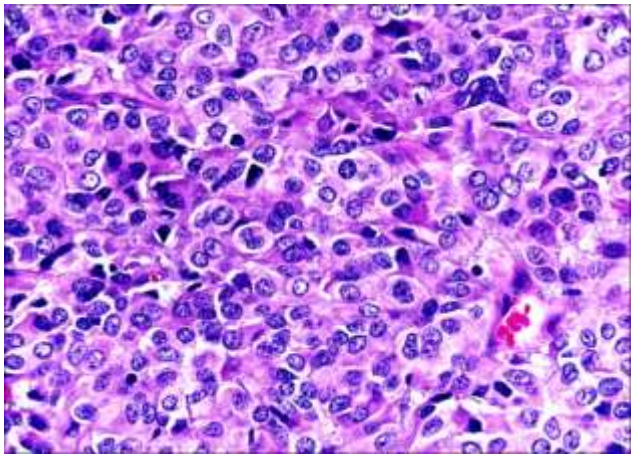
Negative: Epithelial, muscle, nerve markers

Mitotic rate/proliferative index

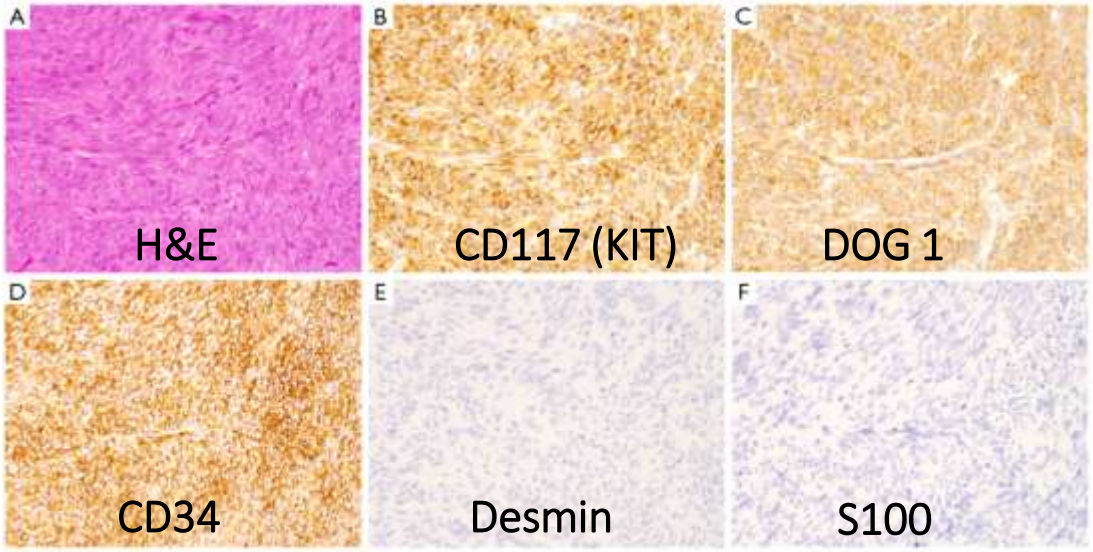
<5, 5-10, >10/5 mm sq (50 HPFs)



Spindle cell GIST



Epithelioid GIST



Malignant lymphoma

Malignant lymphomas

Approximately 5% of all cancers in the USA are lymphomas

90% are of B cell lymphomas
10% are T cell lymphomas
<1% are histiocytic lymphomas

Hodgkin Lymphoma is regarded as B cell lymphoma

Hodgkin lymphoma is nodal disease (100%),
NHL is mostly (90%) nodal but (10%) are extranodal

Approximately 40% of extranodal lymphomas occur in the digestive system with 60% being in the stomach

Pathophysiology of malignant lymphomas

Hodgkin lymphoma spreads in an orderly stepwise fashion

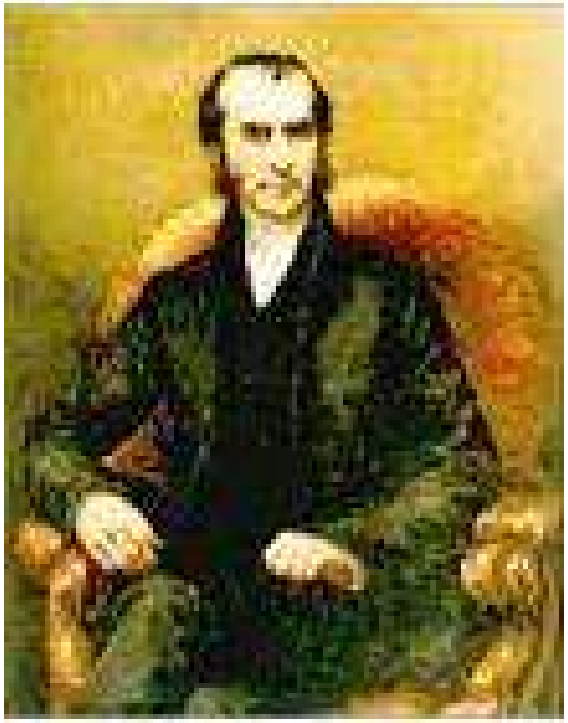
NHL disseminate widely and unpredictably

Lymphoma cells tend to recapitulate the behavior of their normal counterparts (express similar markers, adhesion molecules and chemokine receptors that govern their homing to certain tissue sites)

Lymphoma cells recirculate through the lymphatics and peripheral blood to distant sites

Most lymphoid tumors are widely disseminated at the time of diagnosis)

Lymphomas are often associated with immune abnormalities (loss of protective immunity and breakdown of tolerance)



Thomas Hodgkin (1798-1866)

Curator of the museum and Guy's Hospital

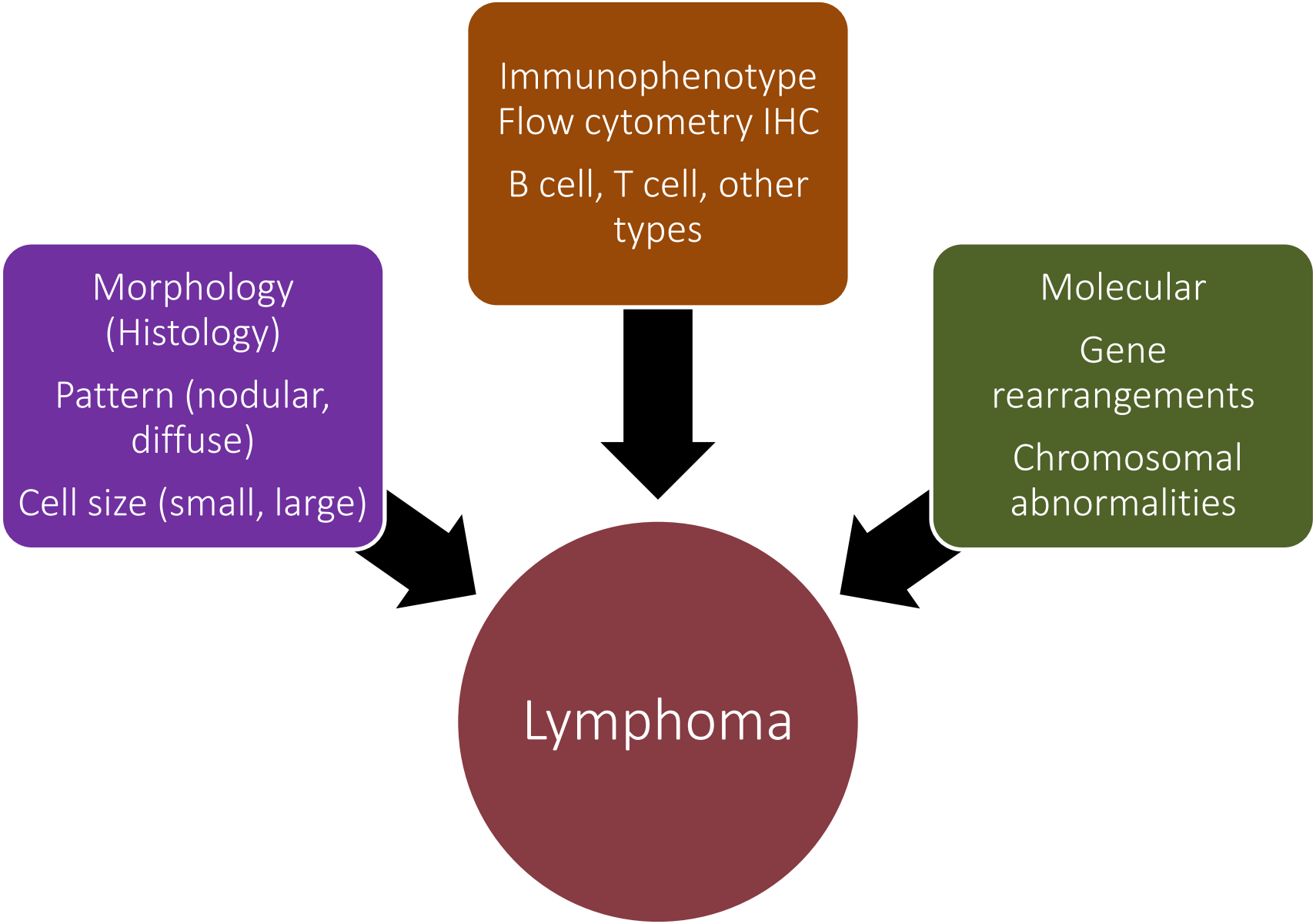
Collected 7 cases of lymphadenopathy

He abandoned practice when he was denied higher position and went on pilgrimage to the Holy Land with his friend Moses Montefiore

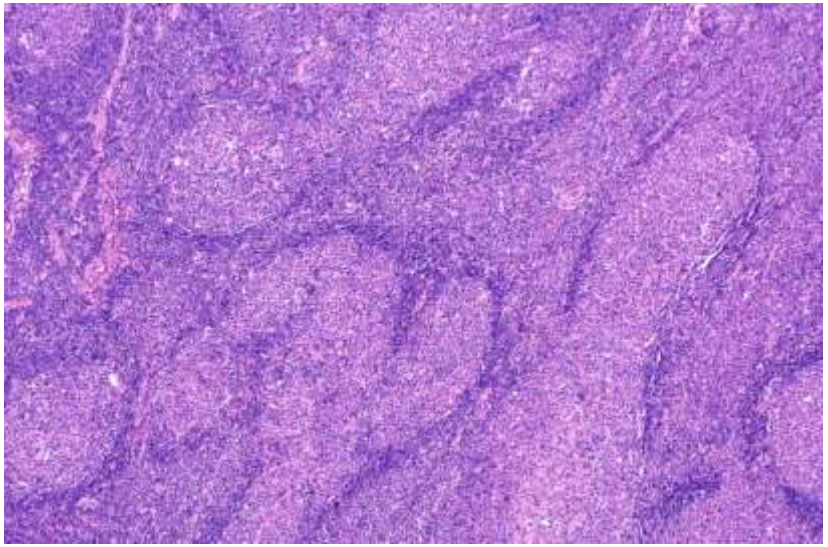
Died of cholera and buried in Jaffa

His 7 cases were recently reviewed;
4 were tuberculosis; 2 were follicular lymphoma;
1 was Hodgkin lymphoma

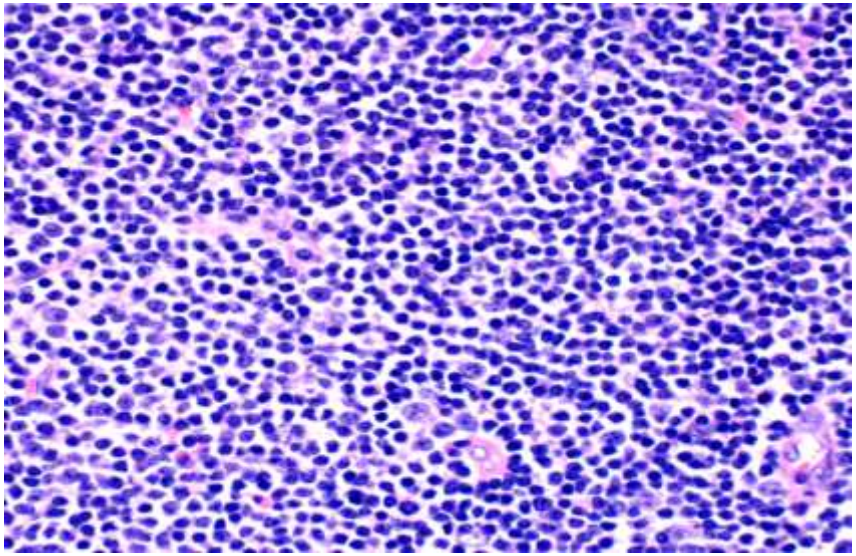
The 3 greats of Guy's Hospital (Thomas Hodgkin, Richard Bright, Thomas Addison)


Immunophenotype
Flow cytometry IHC
B cell, T cell, other types
Morphology (Histology)
Pattern (nodular, diffuse)
Cell size (small, large)
Molecular
Gene rearrangements
Chromosomal abnormalities
Lymphoma

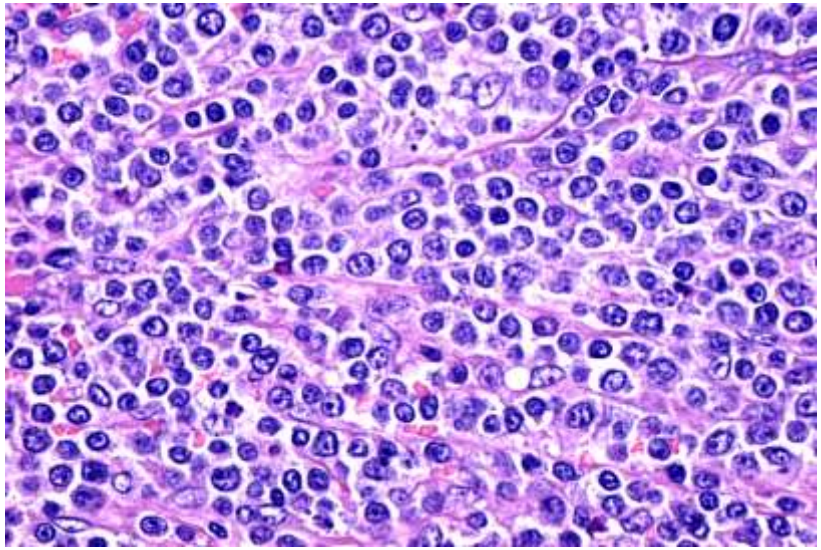
Non-Hodgkin lymphoma morphological patterns



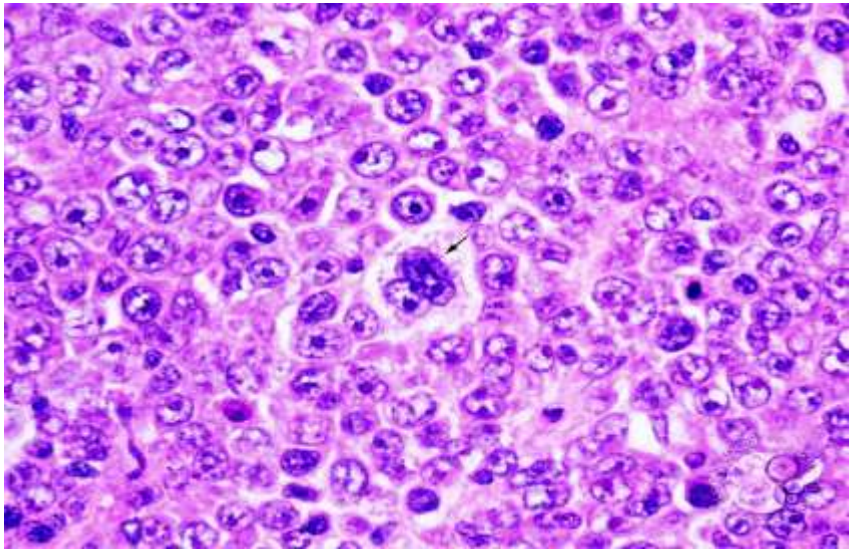
Follicular



Diffuse



Small cell



Large cell

GI Malignant lymphomas
Not all lymphomas occurring in the GI originate in the digestive system

GI specific lymphomas	Lymphomas regularly occurring in the GI
MALT lymphoma (MZL)	Diffuse large B cell lymphoma (DLCBL)
Enteropathy associated T cell lymphoma (EATL)	Follicular lymphoma
Intestinal T cell lymphoma NOS	Mantle cell lymphoma
Duodenal follicular lymphoma (DFL)	Burkitt lymphoma
Other types	Other types

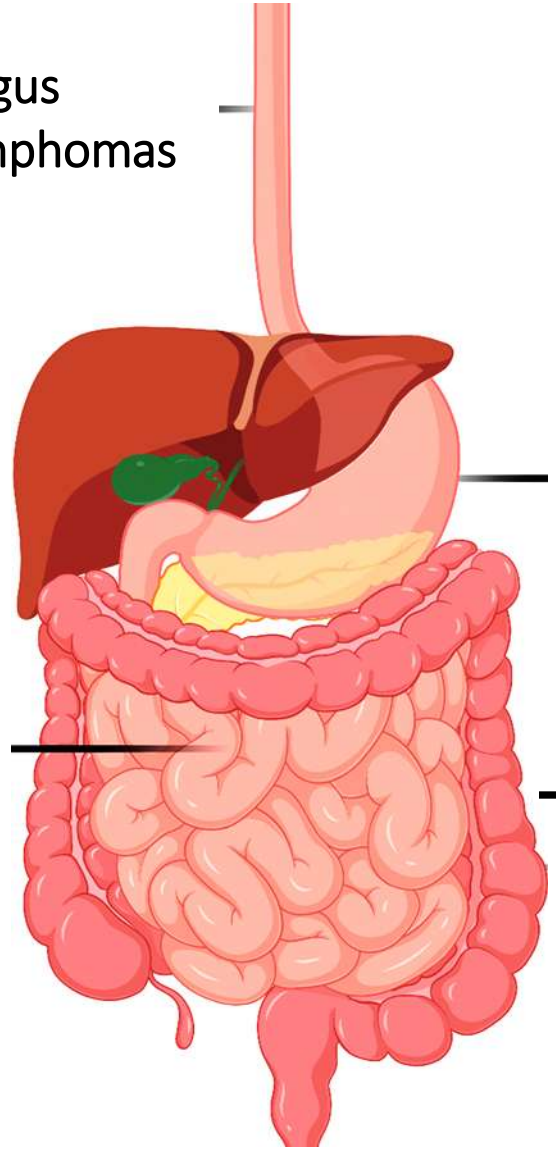
Diagnostic criteria for Primary GI Lymphoma (Dawson criteria)

- Confined to the bowel wall with limited direct involvement of the adjacent mesentery and limited lymph node involvement in the immediate vicinity of the GI tumor

- No peripheral, retroperitoneal or mediastinal lymphadenopathy permitted

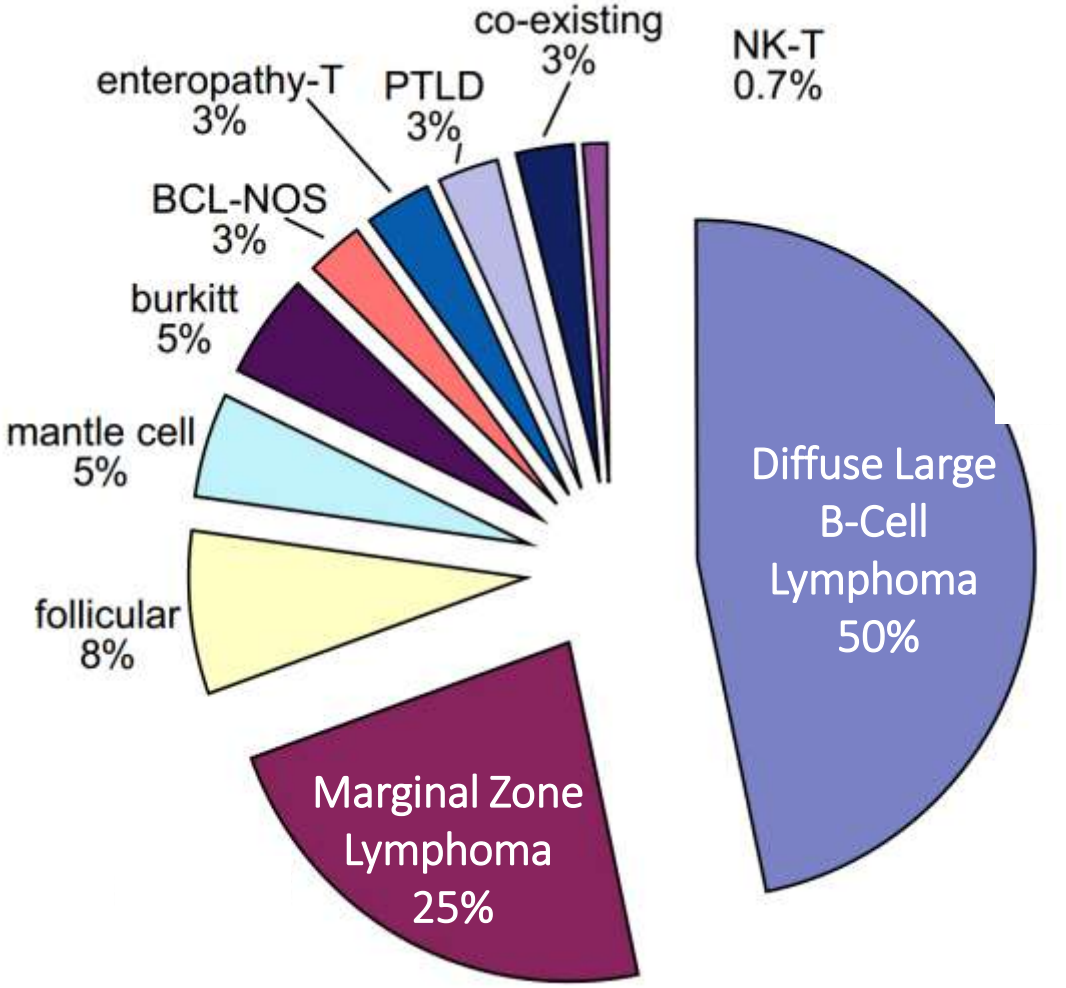
- Normal white blood cell count (no leukemia)

- No involvement of liver and spleen



Diffuse Large B-Cell Lymphoma (DLBCL); Marginal Zone Lymphoma (MALT); Follicular Lymphoma (FL); Duodenal-type follicular lymphoma (DFL); Mantle Cell Lymphoma (MCL); Burkitt Lymphoma (BL)

GI lymphomas by morphology

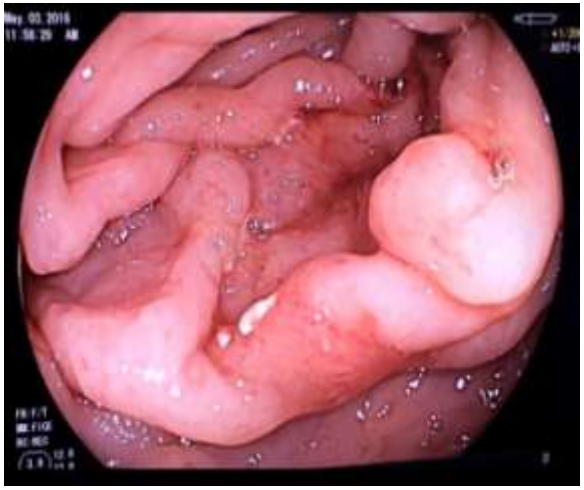


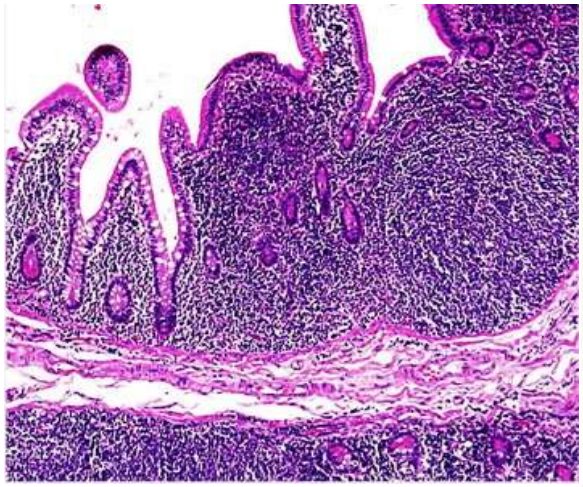
Diffuse Large B-Cell Lymphoma (DLBCL); Marginal Zone Lymphoma (MALT); Follicular Lymphoma (FL); Mantle Cell Lymphoma (MCL); Burkitt Lymphoma (BL); Enteropathy-Associated T Cell Lymphoma (EATL); Post-Transplant Lymphoproliferative Diseases (PTLD)

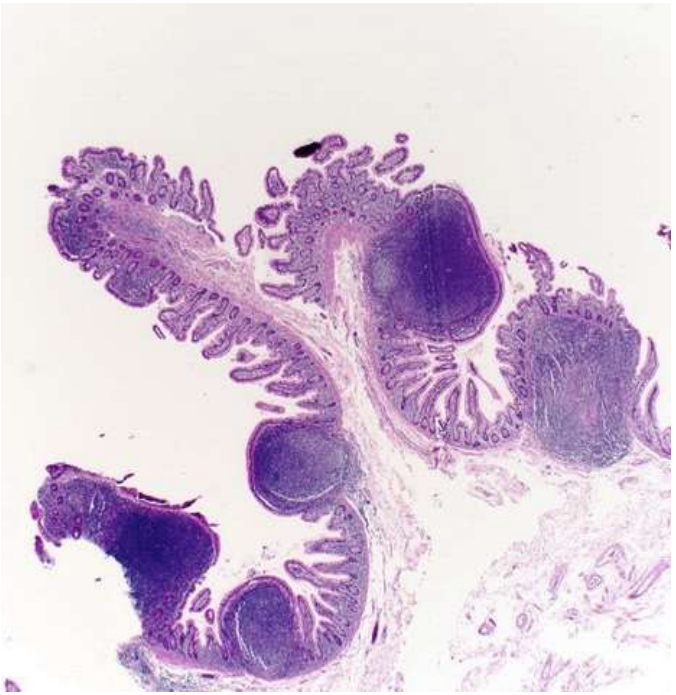
Clinical manifestations of GI lymphomas
Symptoms are similar, regardless of subtype

Abdominal pain (60%), GI bleeding (30%), GI perforation (5%), B symptoms (30%)

Lymphomatous polyposis (10%)







Risk factors for GI lymphomas
Chronic antigenic stimulation and immunosuppression

Helicobacter pylori infection (stomach)

Campylobacter jejuni infection (small bowel)

HIV infection

EBV infection

CMV infection

HBV infection

HTLV-1 infection

Celiac disease

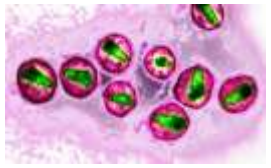
IBD

Posttransplant lymphoproliferative disease (immunosuppression)

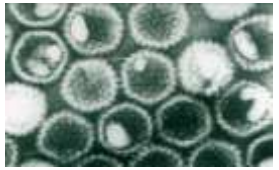
HP

CJ

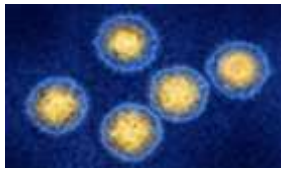
HIV



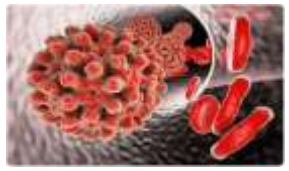
EBV



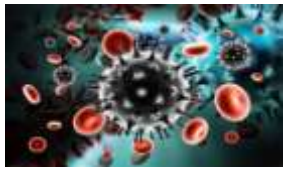
CMV

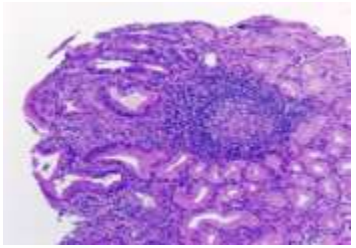


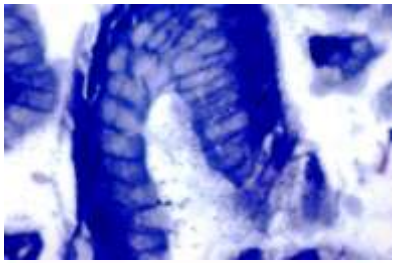
HBV



HTLV1







Direct antigen stimulation

Benign MALT tissue

Chronic *H. pylori* infection

~65%

~30%

Acquired MALT

H. pylori-specific T cells

Trisomy of chromosomes 3,12,18
Allelic imbalance

~5%

H. pylori-dependent

Early-phase MALT lymphoma

LG lymphoma

H. pylori-independent

Late-phase MALT lymphoma

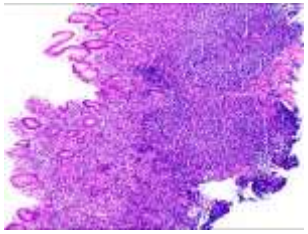
t(1;14)/Ig–BCL10 MALT lymphoma

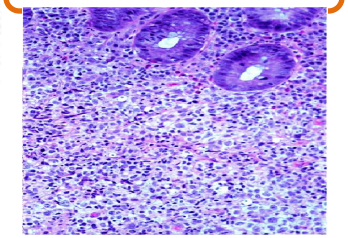
t(11;18)/API2–MALT1 MALT lymphoma

TP53 inactivation
CDKN2A inactivation

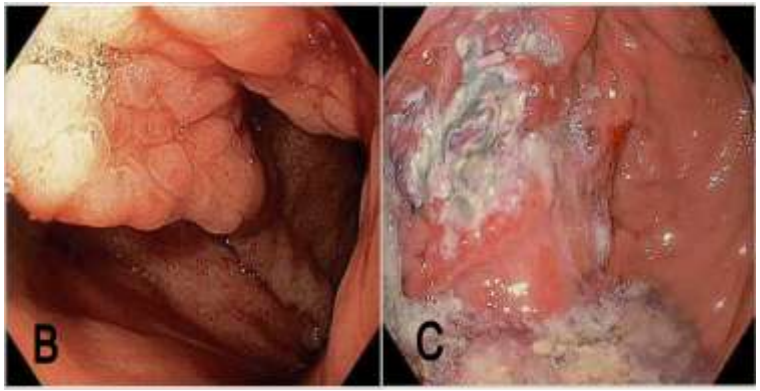
Transformed MALT lymphoma

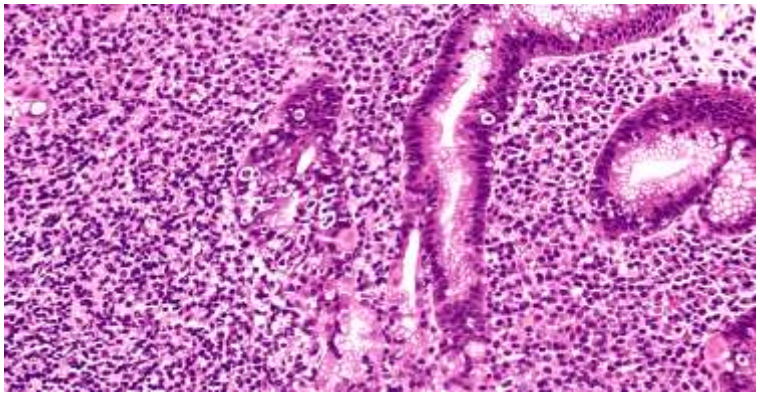
HG lymphoma

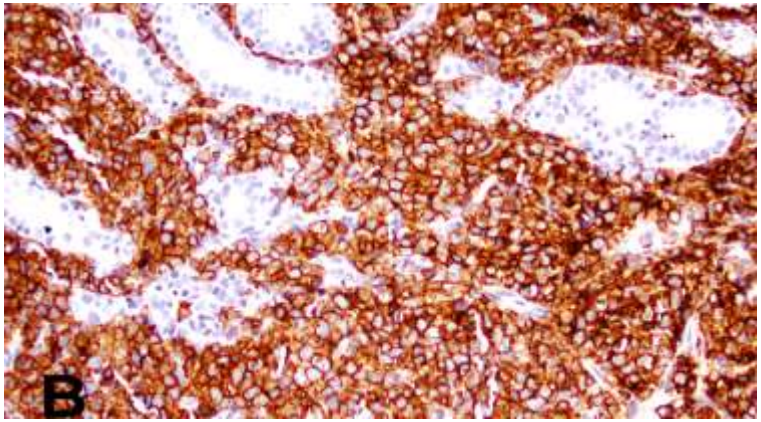




Pathogenesis of H pylori dependent gastric MALT (marginal zone) lymphoma







No specific marker for MALT lymphoma
CD20 (B cell marker) is positive

Marginal Zone Lymphoma (MZL) or Mucosal Associated Lymphoid Tissue (MALT) Lymphoma

90% of GI MALT lymphomas occur in the stomach

90% of gastric MALT lymphoma arises in a background of chronic H. pylori chronic

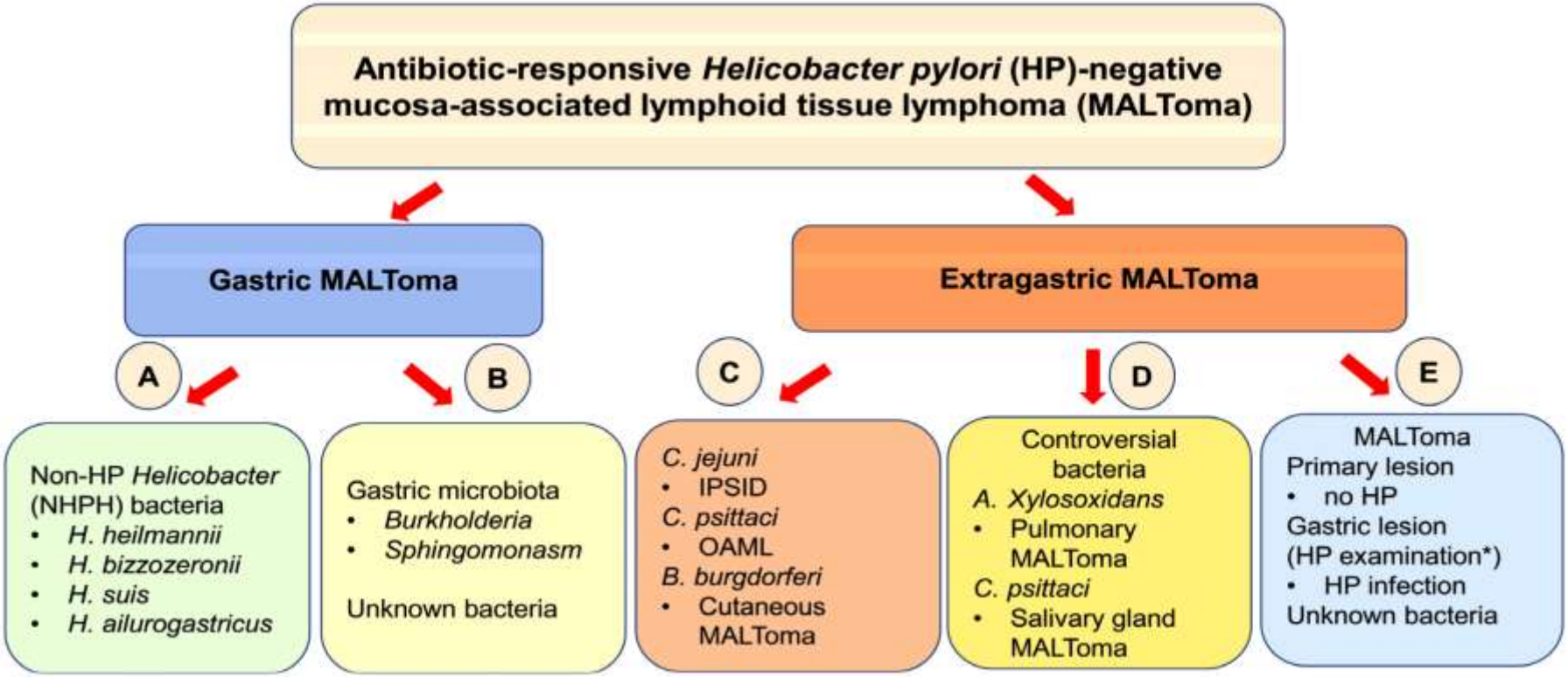
H pylori infection stimulates release IL-2 from T cells which leads to B cell recruitment and proliferate

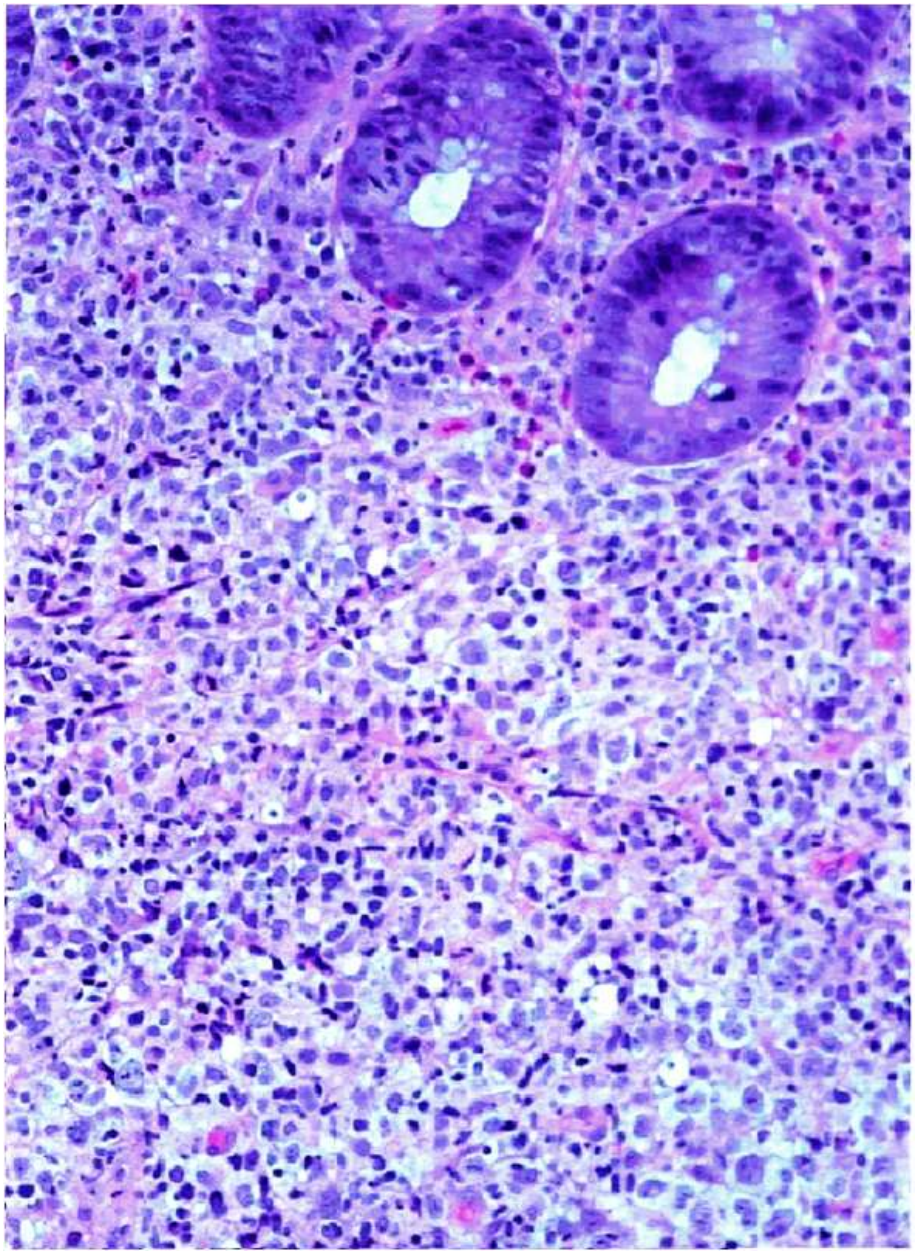
Proliferating lymphocytes can give rise to MALT lymphoma

Most MALT lymphomas are low-grade and cells are CD20 and BCL2 positive (BCL2 is reduced or lost in HG MALT lymphoma)

75% H pylori dependent lymphomas respond to antibiotic therapy

Transformation to a high-grade lymphoma (DLBCL) occurs late


Antibiotic-responsive *Helicobacter pylori* (HP)-negative mucosa-associated lymphoid tissue lymphoma (MALToma)
Gastric MALToma
Extragastric MALToma
A
B
C
D
E
Non-HP *Helicobacter* (NHPH) bacteria
• *H. heilmannii*
• *H. bizzozeronii*
• *H. suis*
• *H. ailurogastricus*
Gastric microbiota
• *Burkholderia*
• *Sphingomonasm*
Unknown bacteria
C. jejuni
• IPSID
C. psittaci
• OAML
B. burgdorferi
• Cutaneous MALToma
Controversial bacteria
A. Xylosoxidans
• Pulmonary MALToma
C. psittaci
• Salivary gland MALToma
MALToma
Primary lesion
• no HP
Gastric lesion
(HP examination*)
• HP infection
Unknown bacteria



Diffuse large B-cell lymphomas (DLBCL)

Most high-grade lymphomas of the stomach are DLBCLs

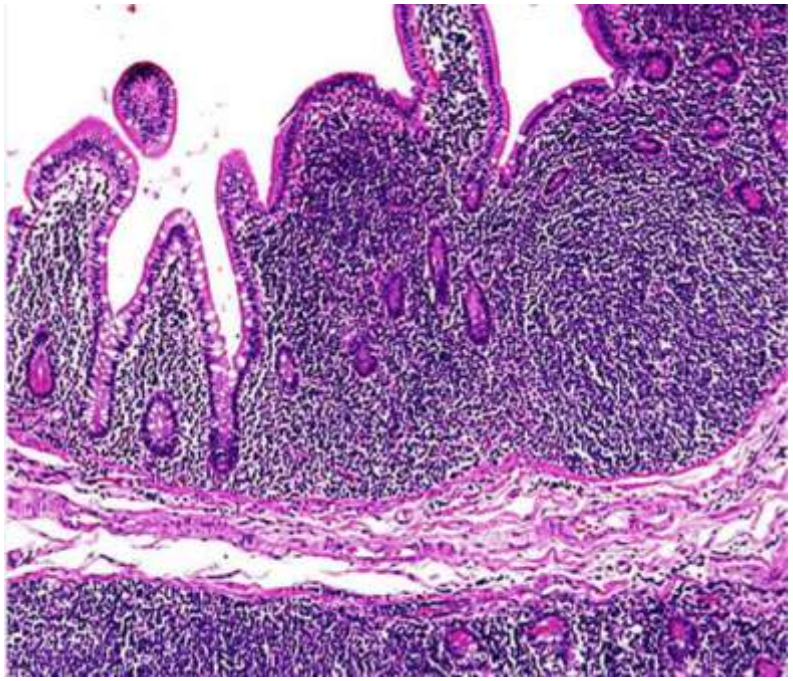
DLBCLs arise either de novo or from transformation of MALT lymphoma

CD20, BCL2, BCL6, MYC are positive

Differential diagnosis includes carcinoma and epithelioid GIST

Markers for carcinoma (cytokeratins) and GIST (c-KIT, GOD 1) are negative

Lymphoid markers (lymphocyte and B cell markers) are positive



Mantle cell lymphomas (MCL)

Involves multiple sites in the GI tract (multicentric) and commonly polypoid (polyposis)

Uniform small to medium sized lymphocytes with round nuclei

Typically Cyclin D1 and CD5 positive

Follicular lymphomas (FL)

Affect small bowel and colon

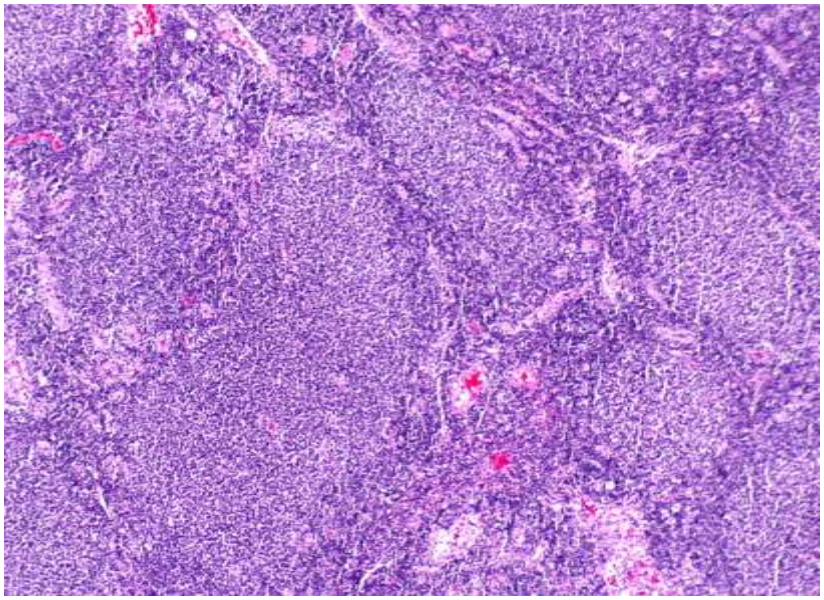
Occur in older adults

May present as multiple polyps (polyposis)

Grading (G1, G2 and G3) is based on the percentage of large cell

Translocations t(14;18) results in BCL2-IGH fusions which results in overexpression of the anti-apoptotic BCL2 protein) is the Hallmark of FL

Tumor cells are CD20, CD10, BCL2 and BCL6 are positive



Duodenal-Type Follicular Lymphoma (DFL)

Uncommon lymphoma B cell lymphoma with strong predilection for the 2nd part of the duodenum

Older adults with an equal M:F ratio

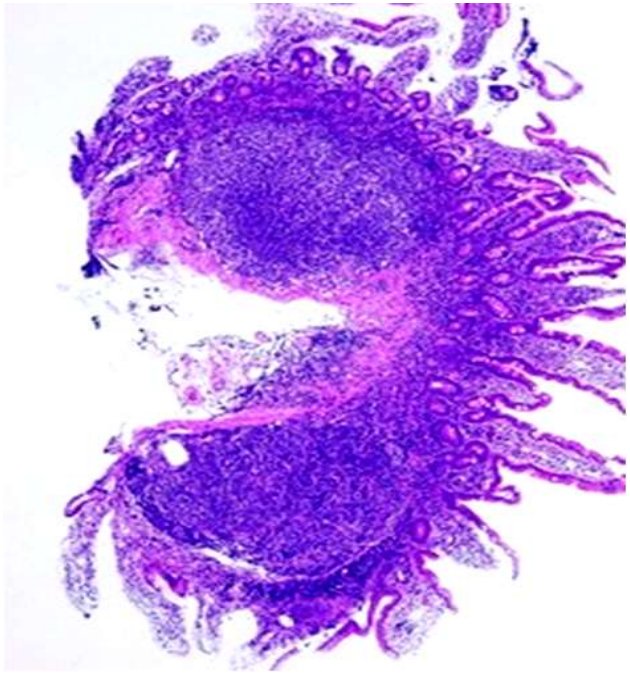
Discovered incidentally during endoscopic examinations performed for other reasons

Low-grade and pursue an indolent course

Similar to non-duodenal-type and nodal follicular lymphomas and sows t(14;18)

Tumor cells positive for CD20, CD10, BCL2 and BCL6

Express α4β7-integrin (homing receptor responsible for T cell migration to the gut)



Burkitt Lymphoma

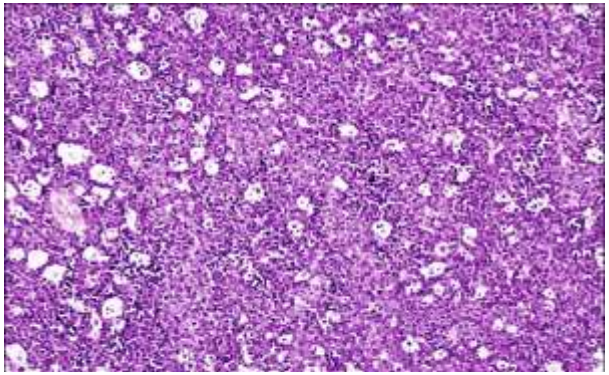
B cell lymphomas occurs in endemic, immunodeficiency-associated and sporadic forms

Associated with EBV infection

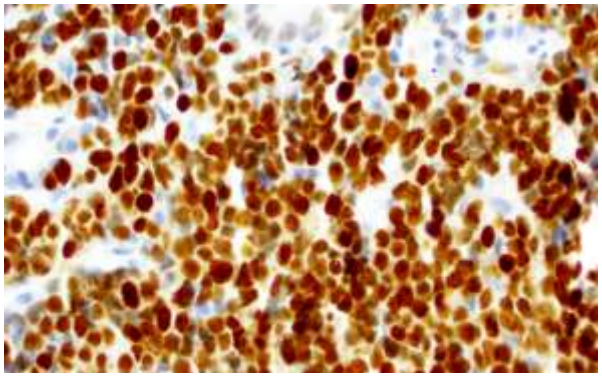
Rapidly proliferating tumor with a brisk mitotic activity with Proliferation Index of 100%

Abundant necrotic cellular debris in macrophages that impart a "starry-sky" appearance

Tumor cells are CD20, CD10, BCL6 and MYC positive



Starry-sky morphology



MYC amplification

Enteropathy-Associated T-Cell Lymphoma (EATL)

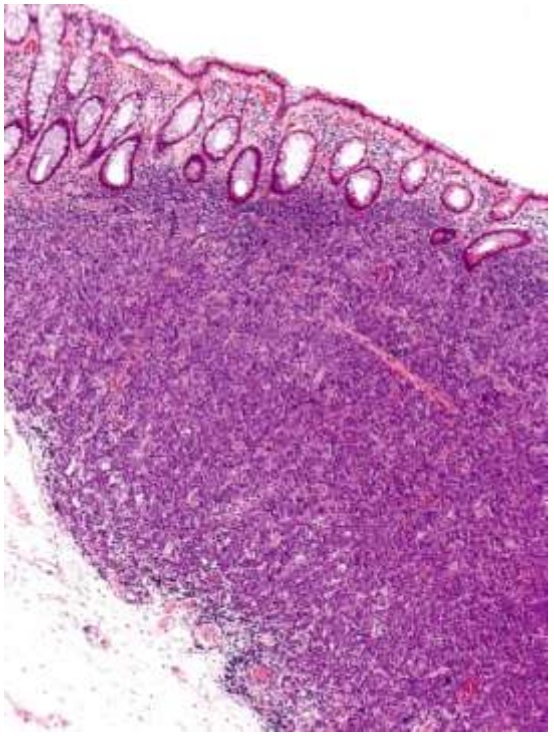
<5% of all GI lymphomas

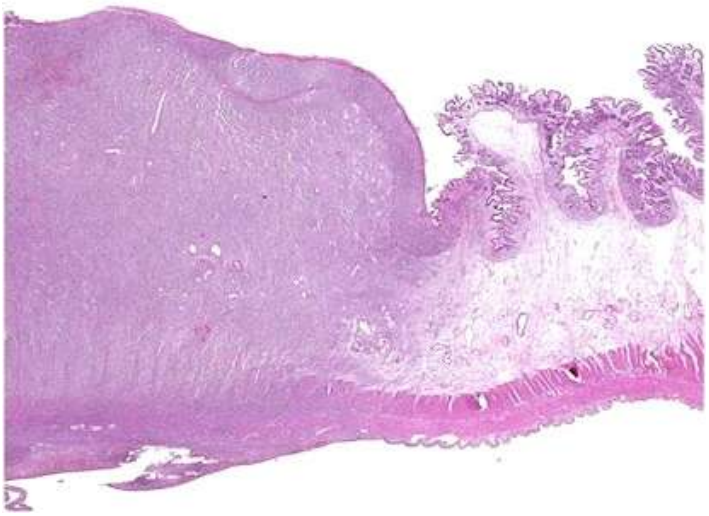
Older adults with history of celiac disease

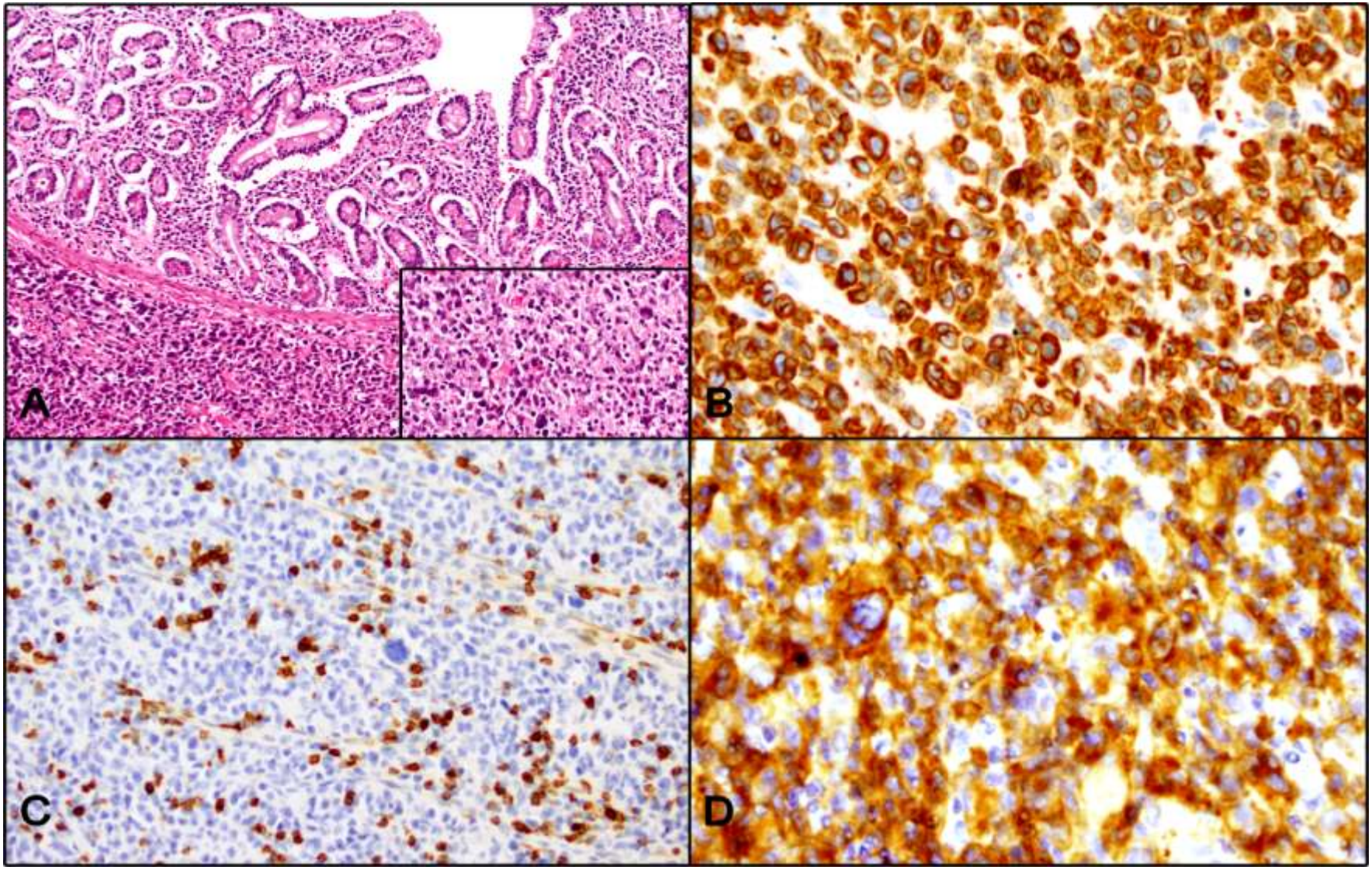
Malabsorptive diarrhea despite gluten withdrawal, abdominal pain, GI bleeding or perforation

Ulcers, masses and diffuse mural thickening

EATL cells express some T cell markers (CD3, CD7, CD30 and CD103)



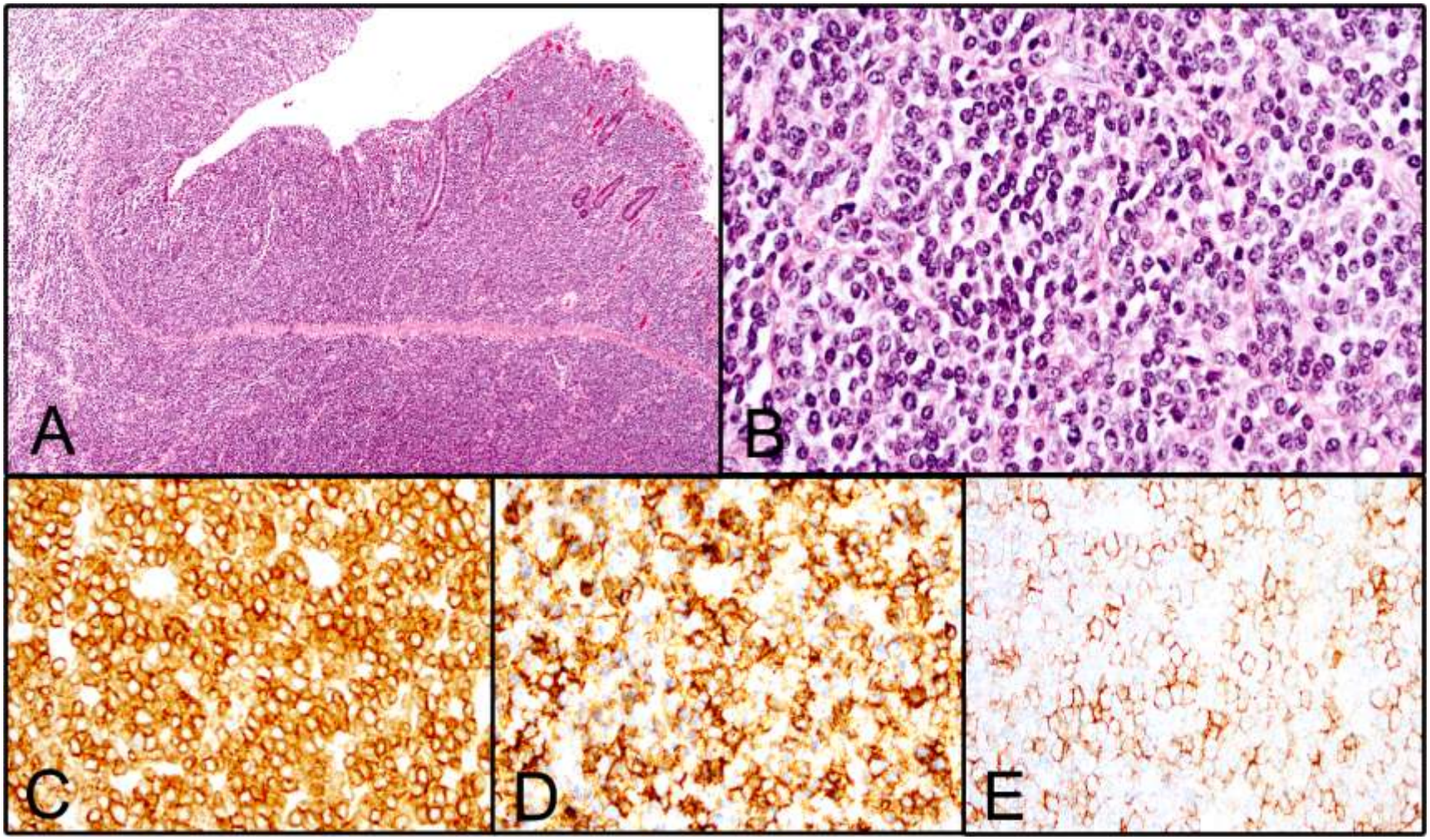




EATL. Panel B: Lymphoma cells are CD3 positive. Panel C: CD5 negative. Panel D: CD30 is positive in large anaplastic cells

Monomorphic epitheliotropic T-cell (MEITL) lymphoma

Aggressive T-cell lymphoma (jejunum and ileum) with no predisposing factors



Monomorphic epitheliotropic T-cell lymphoma. A, Diffuse transmural infiltrate composed of small mature lymphoid cells. B, Monotonous cells with clear cytoplasm. C, By IHC, neoplastic lymphoid cells are diffusely positive for CD3, (D) CD8, and (E) CD56

Intestinal T-cell lymphomas NOS

Usually unifocal plaques or polypoid masses

Not associated with celiac disease

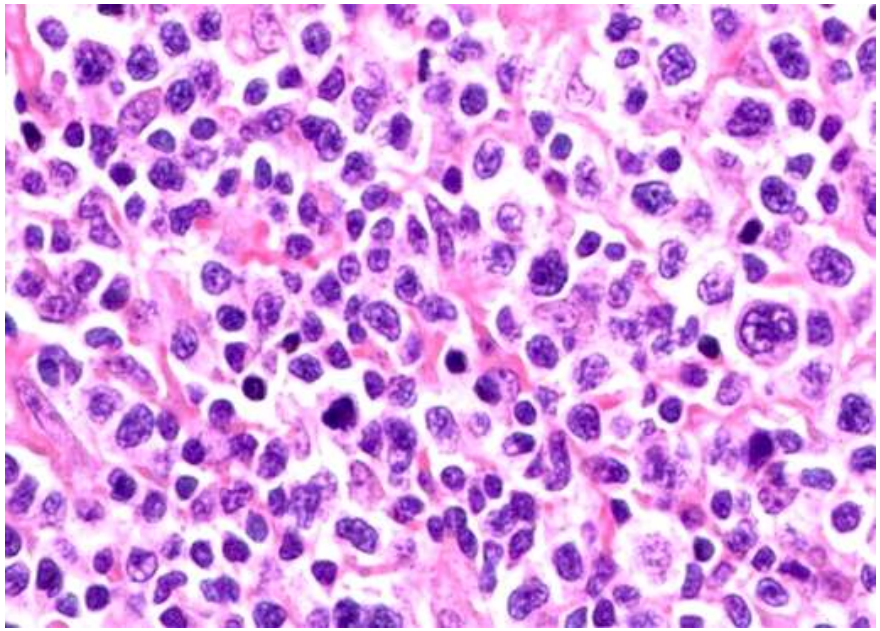
Pleomorphic large cells with necrosis and mitoses

No lymphoepithelial lesions (tumor cells within the epithelium)

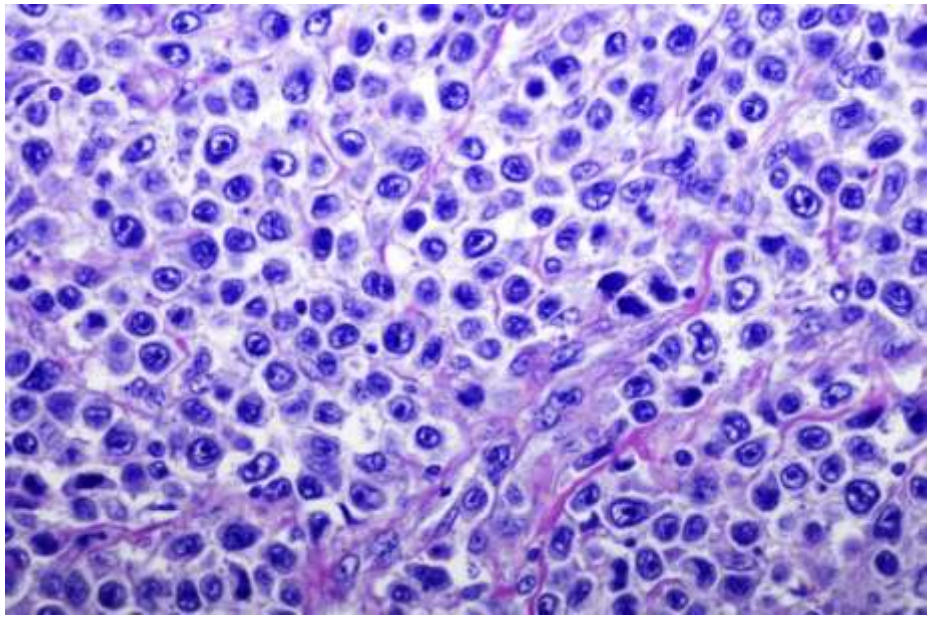
Approximately 10% of tumors are related to **EBV**

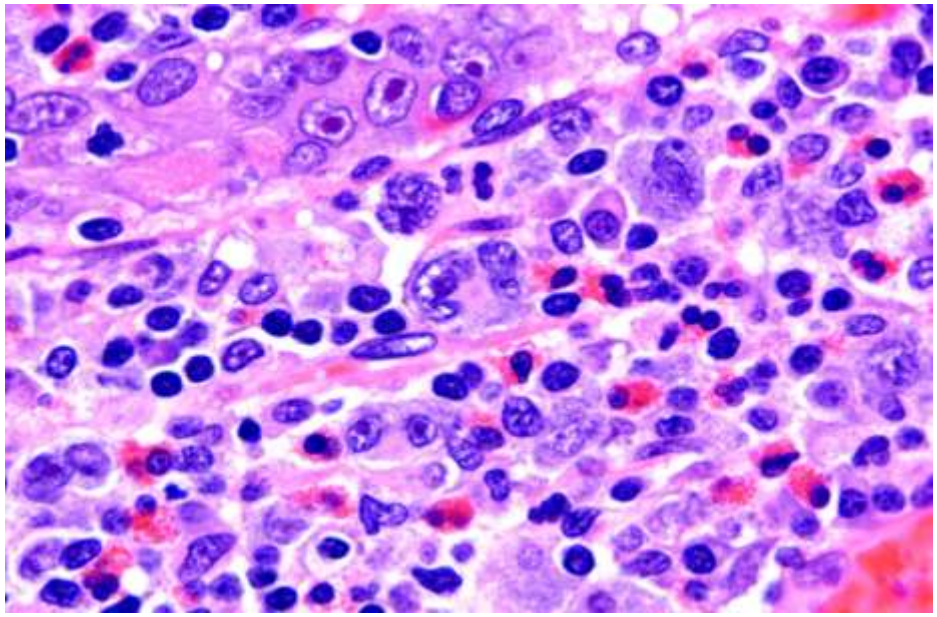
T cell marker (CD4) is positive

Aggressive clinical course

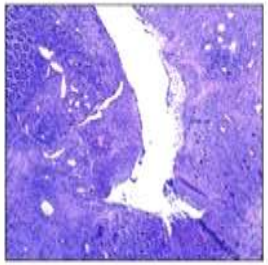


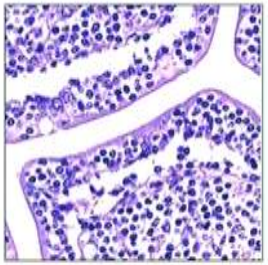
Intestinal T-cell lymphoma NOS

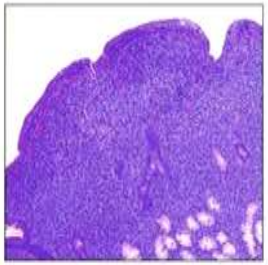


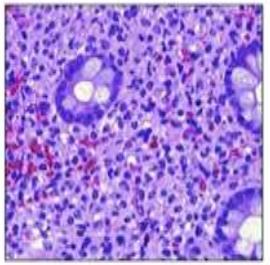


Unique GI Tract T cell lymphoma









	EATL	MEITL	IT-LPD	NK-ENT
Common sites	• Jejunum • Ileum	• Jejunum • Ileum	• Duodenum • Jejunum • Ileum • Colon	• Stomach • Duodenum • SB, Colon
Clinical	• Celiac disease • Aggressive	• No predisposing factors • All ethnic groups • Aggressive	• Indolent • Slight risk of transformation • CD4 > CD8	• Indolent • No transformation reported

Enteropathy associated T-cell lymphoma (EATL), Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), Indolent T-cell lymphoproliferative disorder (IT-LPD), Extranodal NK/T-cell lymphoma (NK-ENT)

Summary of GI lymphomas

- **Primary GI lymphoma is uncommon** (10% of all lymphomas and 40% of all extranodal NHL are in the GI)
- The GI is the **most commonly involved site in extranodal lymphoma**
- Lymphomas can be **B-cell, T-cell or NK/T cells in origin**
- The most common lymphomas are **diffuse large B-cell lymphoma (50%) and marginal zone lymphoma (25%)**
- There are **well-known risk factors for GI lymphomas**; some affect treatment
- Most frequent sites of occurrence are the **stomach, small intestine and ileocecal region**
- Some GI lymphomas, especially the T-cell lymphomas are a **therapeutic challenge**

That's not all Folks!